

77

POSTGRADUATE MEDICINE

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FEBRUARY 1948

Special articles in this issue

TECHNIQUES AND METHODS FOR THE "OCCASIONAL" METASTASIS

Alphonse M. Waters, M.D., UNIVERSITY OF WISCONSIN MEDICAL SCHOOL, MADISON

RESECTION AND PRIMARY ANASTOMOSIS FOR LESIONS OF THE LEFT PORTION OF THE COLON

**John M. Waugh, M.D., MAYO CLINIC; and
Leonard D. Custer, Jr., MAYO FOUNDATION,
ROCHESTER**

NEW DRUGS IN THE TREATMENT OF ALLERGIC REACTIONS

Samuel M. Feinberg, M.D., NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO

Diagnostic Clinics

THE ACUTE ABDOMEN: ROENTGENOGRAPHIC AIDS IN DIAGNOSIS

Leroy Sante, M.D., ST. LOUIS UNIVERSITY SCHOOL OF MEDICINE

THE XIPHISTERNAL CRUNCH

Myer Solis-Cohen, M.D., UNIVERSITY OF PENNSYLVANIA GRADUATE SCHOOL OF MEDICINE, PHILADELPHIA

Scientific Exhibit

TRANSSTHORACIC VAGOTOMY FOR PEPTIC ULCER

K. S. Grimson, M.D., et al., DUKE UNIVERSITY SCHOOL OF MEDICINE, DURHAM, NORTH CAROLINA

COMPLETE TABLE OF CONTENTS ON PAGE 3

Interstate Assembly—Public Auditorium, Cleveland, Ohio, November 9 to 12, 1948, 33rd Year

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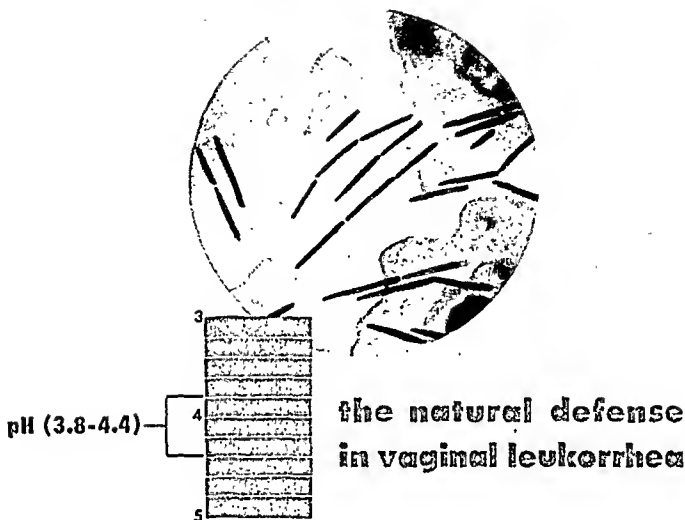
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Table of Contents.

VOL. III, No. II

Special Articles

- DRUGS AND METHODS FOR THE "OCCASIONAL" ANESTHETIST.
Ralph M. Waters, M.D. 77
- RESECTION AND PRIMARY ANASTOMOSIS FOR LESIONS OF THE
LEFT PORTION OF THE COLON.
John M. Waugh, M.D., and Monford D. Custer, Jr., M.D. 85
- NEWER DRUGS IN THE TREATMENT OF ALLERGIC DISEASES.
Samuel M. Feinberg, M.D. 92

Diagnostic Clinics

- THE ACUTE ABDOMEN: ROENTGENOGRAPHIC AIDS IN DIAGNOSIS.
Leroy Sante, M.D. 102
- THE XIPHOSTERNAL CRUNCH.
Myer Solis-Cohen, M.D. 109

Clinical Photography

- CHOLECYSTOGRAPHY IN DIAGNOSING SMALL CALCULI AND STONES.
Adolfo J. Burlando, M.D. 114

Scientific Exhibit

- TRANSTHORACIC VAGOTOMY FOR PEPTIC ULCER.
K. S. Grimson, M.O., et al 116

Research Report

- EFFECTS IN ANIMALS FOLLOWING INOCULATION OF ALPHA
STREPTOCOCCI ISOLATED IN STUDIES OF EPILEPSY AND
SCHIZOPHRENIA, II.
Edward C. Rosenow, M.D. 124

Departments

- BOOK OF THE MONTH. *Internal Medicine in General Practice* 137
- MEN OF MEDICINE. Archer Chester Sudan, M.D. 139
- EDITORIALS. *Training and Qualification of an Internist • Mid-Year A.M.A. Meeting •
Talcum Powder Granuloma* 144
- THIS MONTH IN MEDICINE. *Zero Hour in Trauma • Lymphogranuloma Venereum and
Pituitaritis • Streptomycin in Tuberculosis • Ulcerative Colitis and Hog Stomach • Penicillin by
Intra-Oral Drip • Acne Rotacea • Penicillin Dosage Schedules • Bagasse Disease* 147
- CONSULTATION SERVICE. *Falciparum Malaria* 150
- NEW DRUGS 151
- MEDICINE MAKES NEWS 153
- CORRESPONDENCE DEPARTMENT 154
- AFTER HOURS 155

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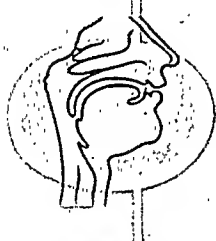
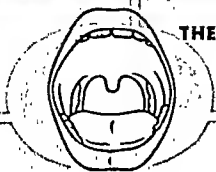
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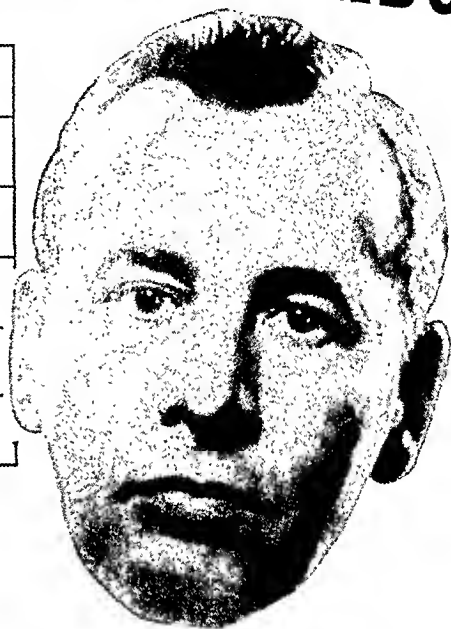
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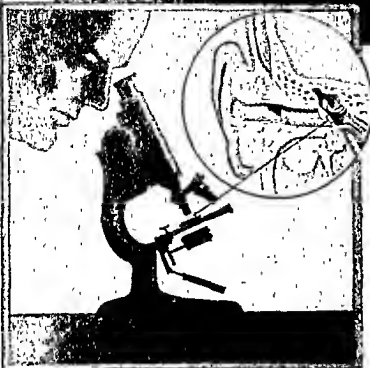
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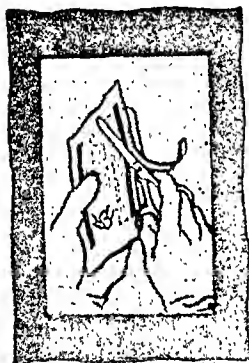
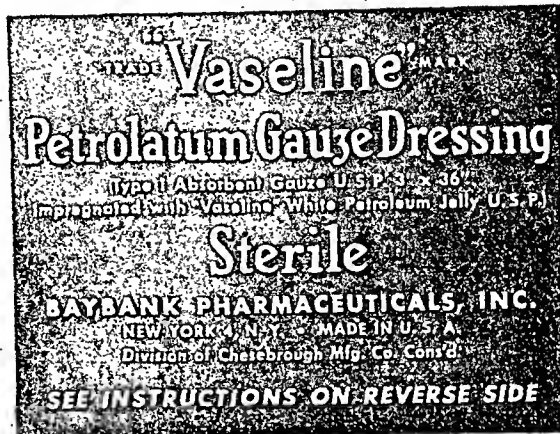
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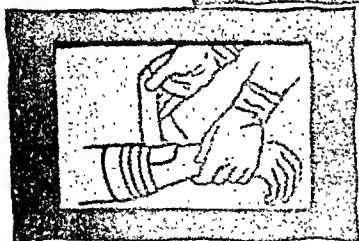
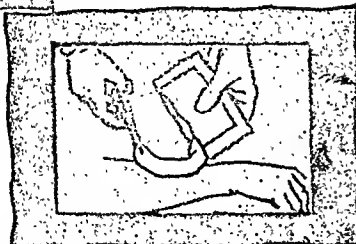


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2. Travel, J. & G. *Contractors on Thursday, Nov. 1978*

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Irritability Associated

With Infections¹

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With Pain^{1,2}

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Chorea
Hysteria
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Mania

Anticonvulsant

Traumatic
Tetanus
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Induction of Sleep

OBSTETRICAL

Nausea and Vomiting
Eclampsia
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SURGICAL

Preoperative Sedation
Basal Anesthesia
Postoperative Sedation

PEDIATRIC

Sedation for:
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Blood transfusions
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Reactions to immunization
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Preoperative Sedation

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*Fishberg, A. M.: Heart Failure, Lea and Febiger, Philadelphia, 1946, p. 733.

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Drugs and Methods for the "Occasional" Anesthetist

RALPH M. WATERS*

UNIVERSITY OF WISCONSIN MEDICAL SCHOOL, MADISON

PREVIOUS to 1900 every graduate of an American medical school was capable of administering the three original inhalational anesthetic agents with reasonable safety. Since 1900 we have learned to use procaine for injection instead of cocaine. We have learned that all anesthetic drugs tend to depress and obstruct respiration. We have learned the means of safeguarding the functions of breathing by careful dosage, by the use of oxygen and artificial airways. Has the necessary equipment for the employment of these safeguards so frightened the modern practitioner of medicine that he no longer has the confidence and competence of his predecessor?

I hope to defend the proposition that the four agents nitrous oxide, ether, chloroform and procaine, with relatively simple apparatus, in the hands of any conscientious and competent physician, can provide safe, pleasant and adequate anesthesia for the majority of the operations in modern surgical practice.

I do not wish to decry in the slightest degree specialization in anesthesia. Nor do I wish to minimize the value of newer drugs and tech-

nics which have been added in recent years. Rather is it my desire to emphasize the importance of a thorough medical training for the administrator of anesthetics and simplicity in method of administration, unless or until the status of true specialization is achieved.

In more recent times anesthesia has been influenced by hollow needles, syringes, and rubber tubing. Pharmacologic and pharmaceutical advances have made many new drugs available. Present methods of marketing assure accuracy of dosage of non-volatile agents. All these refinements tempt us to complicate our technics. As a result we are now blessed (and sometimes cursed) with rectal, hypodermic, intravenous, and perineural administration of a great number of drugs, alone and in combination, to produce either local or systemic anesthesia or both simultaneously.

Since all anesthetic agents may and frequently do cause serious depression of the respiratory and other functions, the problems of modern anesthesia grow ever more complicated. To determine the cause and the proper treatment of a condition arising after the simultaneous administration of an opiate and a barbiturate followed by a spinal anesthetic and perhaps further supplemented by the inhalation of nitrous oxide and the injection of some curare-

*Professor of Anesthesiology, University of Wisconsin Medical School, Madison.

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like substance is indeed a difficult task. The opiate may have relaxed muscles around the pharynx resulting in respiratory obstruction; the barbiturate may have abolished the carotid mechanism through which lack of oxygen causes a compensatory increase in breathing; the spinal may have paralyzed some of the respiratory muscles; the tension of oxygen in the inspired nitrous oxide may have been too low or the effect of curare may have constricted the lumen of the bronchi.

To determine the cause of trouble in such circumstances may be difficult or impossible for the most experienced specialist. To treat the condition satisfactorily may necessitate a rapid application of technically difficult maneuvers whereby, through a process of elimination of possible causative factors, the guilty one is identified and safe conditions are restored. The terms "premedication" and "basal narcosis" have become very common in our more recent anesthetic vocabulary. We ought to be very sure that such practices are employed to increase the safety and well-being of the patient and not to promote our own convenience or to "cover up" careless or inexperienced treatment in the operating room.

You will gather from what I have just said that effects of several different sedative and anesthetic drugs, acting upon one patient simultaneously require a maximum of skill, experience, and knowledge in management if safety is preserved. It is for this reason that I suggest to those who must administer the occasional anesthetic—the student, the intern, the general practitioner, the young surgeon, and the embryo specialist—that each ought to begin by learning about a minimum number of drugs and methods. After mastery of these, he may wisely proceed to more complex efforts. Combinations of drugs and complicated apparatus, and I might add methods temptingly easy of application, do not compensate for lack of basic knowledge, skill and experience. In the hands of the neophyte, they do contribute numerous dangers, embarrassments, and even tragedies.



RALPH M. WATERS

IMPORTANCE OF MEDICAL BACKGROUND AND TRAINING

Had our predecessors realized what a multiplicity of drugs and complexity of technics were to become available in this century, it is difficult to believe that they would have permitted anesthesia to drift outside the practice of medicine in America and become a technical procedure. It was, perhaps, the simplicity of the drugs and methods in common use at the end of the 19th century which caused so large a number to feel that professional respect and economic support for the doctor who administered anesthetics were not justifiable.

The staff and the management of many hospitals of the United States came to look upon anesthesia as a technical matter only. Many of our schools all but ceased to teach anything about anesthesia. The hiatus thus left in the product of our medical education was doubtless a major cause of the former neglect of anesthesia. Neglect rests undisturbed in an atmosphere of ignorance. But a realization of our

former false position has been growing for many years. Ignorance is being dispelled and neglect has now been supplanted by recognition and encouragement.

We now appreciate that a physician who is familiar with the principles and skillful practice of anesthesia can be useful in a rather broad field. His aid is sought in the treatment of pain whatever its cause. Not infrequently his efforts shed some light upon diagnostic problems. In many hospitals, he is consulted regarding the care of acute respiratory and circulatory disorders. Inhalational therapy and even the intravenous administration of fluids are considered a responsibility of the department of anesthesia in some institutions.

However, good teachers and adequate methods of instruction cannot be pulled out of a hat by magic. Our medical schools and larger hospitals are trying, almost frantically in some instances, to establish adequate instruction and service in anesthesia. We have now come to a pretty general realization of the fallacy of the premise that the administration of anesthetic drugs and the supervision of patients affected by them is anything other than the practice of medicine. The demand for physicians who are expert in this branch of our profession, both as teachers and as private practitioners, now far exceeds the supply.

AT PRESENT the importance of certification of specialists; of long term residencies in all branches of practice, including anesthesia, is being stressed—if not overstressed. Even small hospitals and small communities are demanding that they be furnished with "certified" anesthetists. A sufficient number of these are not now available. It is my belief that, for the vast majority of operations performed in our smaller hospitals, full-time specialists with several years of formal training are not essential. It is also my opinion that after brief instruction and practice in a few technical details, a physician, with his knowledge of modern medicine and all that it implies, is far safer as an anesthetist than is a non-medical person

however carefully trained in technical manipulation and use of anesthetics.

The scope of the anesthetist's work interlocks with every phase of modern medical practice. The medical foundation is hard to acquire, not the technical tricks. The three drugs and the simple methods commonly used previous to 1900, and the administration of which was familiar to every doctor, are still available. These together with the rational use of procaine cover our everyday needs.

I suggest that, with interest and attention to the subject, there are in every community an adequate number of physicians who can quickly learn to use these drugs to the satisfaction of everyone. To induce them to do so, they must be encouraged and supported by hospitals and the profession; because it was lack of such encouragement and support which, in former years, almost forced anesthesia out of the practice of medicine.

Every present-day physician is familiar with the physiology of respiration and circulation. It is necessary to re-interpret this knowledge to form a practical concept of various aspects of the transport of oxygen, carbon dioxide, and the anesthetic agents to and from the central nervous system. Intelligent management of all anesthetized patients requires this knowledge so re-interpreted. In addition, there are a few simple technical tricks which can be acquired by experience. A better and quicker way to acquire them is by association and practice with an experienced specialist who is in addition a good teacher.

Every full-time anesthetist ought to be willing to teach the simple fundamentals to other physicians. Often the occasional anesthetists whom he helps may become his junior associates and assistants. Certainly all departments of anesthesia in our large institutions should maintain short periods of instruction aimed to benefit the occasional anesthetist.

The foundation of sane management in anesthesia is the ability to maintain free and adequate breathing and quickly to recognize obstruction and depression of respiration and their secondary effects upon circulation. Early

discovery and correction is important. Here, if ever, "an ounce of prevention is worth a pound of cure." The familiar quotations are apt that "anoxia begets anoxia" and that "anoxia not only stops the machine but wrecks the machinery."

Compressed oxygen is now generally available in operating rooms. The occasional anesthetist will find it to his advantage to become familiar with methods of reducing oxygen to atmospheric pressure and of administering it. The necessary simple mechanical knowledge can be acquired in an hour or two. The early acquisition of skill in the use of artificial airways, both pharyngeal and laryngeal, is of great importance.

The other essential acquisition of the physician who intends to administer an occasional anesthetic is familiarity with one means, for each of a very few drugs, of controlling the dose within safe limits. Mastery of the technic of a simple and complete field block with procaine is essential. Any textbook will explain the common methods. It is well to choose one simple means of using each drug and employ it exclusively until it is mastered, rather than to try several methods and become confused. A few lessons from an experienced teacher who is not "too modern" will be helpful.

Familiarity with the use of oxygen in a simple mask and breathing bag is essential. The dangers and disasters of anesthesia follow interruption of the transport system. Quick establishment of a free airway to the alveoli and artificial respiration if necessary are the remedies. This is true whether the guilty drug be inhaled or injected and regardless of where it is injected.

It seems reasonable therefore that the beginner or the occasional anesthetist will be more ably equipped if he masters the different inhalational methods first.

My associates and I have studied many new agents and methods during the past twenty years. The original three drugs often served as controls for such experiments. Obviously, for fair comparison, administration of the older agents was accompanied by as free breathing,

TABLE 1
INCIDENCE OF ABNORMAL HEPATIC
FUNCTION AFTER OPERATION

ANESTHETIC	PER CENT OF CASES
Chloroform	52
Ether	60
Cyclopropane	60
Spinal	66
Pentothal	55
Avertin	33

as careful dosage and as much enrichment of respired atmosphere with oxygen as is used with newer drugs.

Comparative statistical evaluation of the clinical results in these cases now convinces us that one, or at most two, of the older agents, administered with equal skill to a particular patient can produce as satisfactory results to surgeon, patient, and anesthetist as are secured by any of the complicated modern methods and combinations. They also require as much skill and effort on our part to produce such satisfactory results.

OPIATES, barbiturates, and tribromethanol (avertin) being respiratory depressants had better be avoided. Saturation with gases or vapors can be much more readily achieved without them. The one non-volatile drug which the occasional anesthetist will find useful is scopolamine in small doses to diminish secretions (or atropin). If non-volatile depressants have not been given, the onset of inadequate breathing during anesthesia can usually be attributed directly to an overdose of vapor, to too great systemic absorption of procaine, or to a lack of oxygen and the appropriate remedy can be applied.

Ethyl chloride, ethylene, cyclopropane, vinyl ether, trichlorethylene, and the newer non-volatile agents vary from the older ones in potency and pharmacologic characteristics. Differences in technical details of their administration tend to confuse the less experienced administrator. They possess no outstanding advantages which skill with nitrous oxide, ether, chloroform, and procaine cannot match. These

drugs, I believe, every doctor ought to be able to administer in a manner acceptable to the patient and the surgeon and with satisfaction to himself. All four are included because they supplement each other. A proper choice of one, or at most two, of the four can be made to serve almost every purpose.

Nitrous oxide, when inhaled for several minutes in concentrations below 60 per cent, abolishes the sensation of pain without producing unconsciousness. Analgesia produced in this manner has a wider application than is generally appreciated. When nitrous oxide is diluted

TABLE 2
65 CASES—CHLOROFORM
AVERAGE

Time	=	120 minutes (45—240)
Total	=	39 cc. (12—103)
Inh.	=	0.55 Vol. per cent (0.23—0.96)
Bl.	=	6.2 mgm. per cent (3.2—12.0)
Bl.O ₂	=	16.2 Vol. per cent (10.3—21)
Bl.CO ₂	=	46 Vol. per cent (39—59.5)

with less than 40 per cent oxygen, and inhaled over a period of several minutes, unconsciousness results, but muscle-tone and reflex activity are not abolished. If used with as much oxygen as normal atmosphere contains and when ample time is allowed for saturation of the blood and tissues, nitrous oxide serves admirably to abolish the pain of brief operations or of those which do not require relaxation of muscles or the absence of reflex activity.

In my estimation, the dangers of nitrous oxide have been greatly exaggerated in recent years. They have certainly been enhanced by the injudicious use of depressant drugs as adjuvants. Nitrous oxide is also convenient for the production of rapid and pleasant unconsciousness preceding and during the induction of ether anesthesia. Experience and skill in making the transition and in permitting the proper accumulation of expired carbon dioxide during such an induction adds to the speed and smoothness of the procedure.

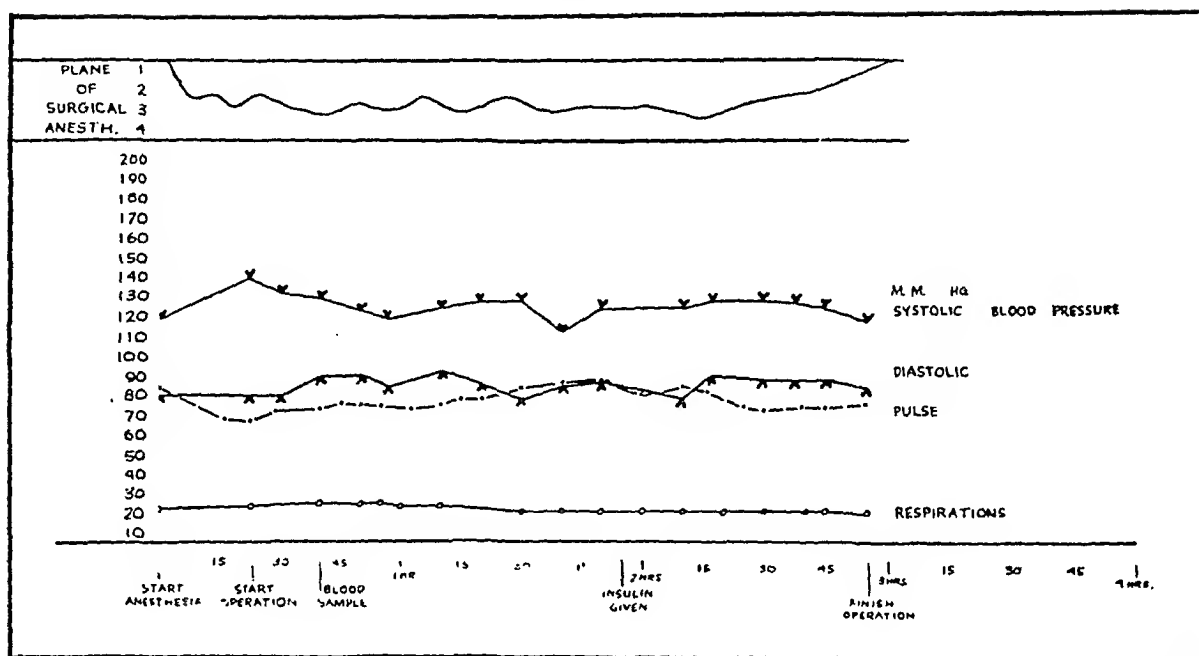
Ether, skillfully administered, can be made to produce satisfactory anesthesia for nearly all operations during which a source of ignition is

not present. Added oxygen, or nitrous oxide mixed with oxygen, enhances the hazard of fire and explosion if a flame, spark, or static charge is anticipated. Slow and gradual changes in the concentration of vapor prevent many of the more common complications. Mucous secretion, struggling, and obstructed respiration during induction can thus be minimized. Failure to saturate with adequate vapor-tension before operation is begun is the usual fault in the administration of ether.

AN INADVERTENT overdose during induction, causing arrest of respiration, rarely needs treatment other than brief interruption of administration. Respiratory arrest during either nitrous oxide or ether anesthesia is rarely serious unless there is simultaneous scarcity of oxygen in the patient's tissues. Confidence that the lungs can be inflated with air or preferably oxygen is the only safeguard necessary. A minimum flow of oxygen under the mask, even with "open drop" technic, is essential to prevent hypoxia.

Chloroform is added to this list of simple drugs for the occasional anesthetist after careful consideration. Obviously on certain occasions, he must be in possession of a completely potent and universally applicable agent which can be used without hazard of fire. The technical dangers with chloroform are great. It seems to me however that they are no greater for the occasional anesthetist than are other means of avoiding the danger of explosions. The administration of tribromethanol by rectum, intravenous administration of a derivative of barbituric acid or blocking of the nerve supply to the region of operation are accompanied by dangers, too. Admittedly, individual skills and the feeling of confidence which goes with them are important. If your confidence lies with one of the methods just mentioned, well and good. However, even in the hands of the relatively inexperienced it is my belief that chloroform can serve adequately and safely.

In the absence of nitrous oxide, chloroform affords a means, agreeable to the patient and



Gastric Resection (Ulcer) January 11, 1947. Male: Age 59; Weight 220 lbs.; 9.6 gm. Hb. Controlled Diabetes. Septic arthritis of hip. Questionable old cardiac infarct. Physical status: poor. Premedication: Morph. Sulph. 1/16 grain & scopolamine 1/200 grain. Chloroform—open drop. (No added oxygen.)

convenient to the anesthetist, of inducing unconsciousness for a brief operation or for the induction preceding ether. Safeguards during the administration of chloroform are, first, patience and deliberation in increasing the vapor-tension; second, constant palpation of the patient's pulse, and third, addition of oxygen to the respired atmosphere.

Maintenance of the freest of free breathing is very desirable. Rapid increase in the concentrations inhaled or a sudden high tension entering the alveoli, due to a deep breath or other cause, may allow a marked increase in tension of chloroform in the blood to reach the heart suddenly. Such injudicious overdose may cause myocardial depression or even cardiac arrest. Ventricular fibrillation, so often mentioned in the literature, is extremely rare in man.

PROMPT artificial ventilation of the lungs, quickly to reduce the alveolar concentration, is the remedy for overdose of chloroform.

Constant palpation of the pulse is important. If one remembers that some thirty seconds intervene between the dropping of liquid chloroform on a mask and the contact of the corresponding vapor-tension with the muscles of the heart, deliberation seems justified. If a sudden change in the pulse is palpated or if respiration is markedly depressed or arrested, interruption of administration and quick ventilation of the lungs with oxygen will restore the heart at once.

Evidence of acute cardiac depression has been observed 12 times by my associates and me at the Wisconsin General Hospital during 1,000 administrations of chloroform. In every instance a relatively sudden and large increase in concentration preceded the depression. On one of these occasions the heart is known to have stopped beating. Prompt inflation of the lungs with oxygen almost instantly restored what appeared to be normal conditions in every instance. What may appear to be almost infinitesimal amounts of chloroform added to nitrous

perience are nevertheless necessary to foresee the physiologic and pharmacologic changes that may result in a patient following such injections. Prompt action, with technically difficult maneuvers, may be necessary at times to restore normal conditions. The beginner must decide for himself the direction of his greatest skill and knowledge. He must aim at maximum safety for his patient with due consideration for the convenience of the surgeon for whom he works.

SUMMARY

It is strange, but nevertheless quite true, that the three anesthetic agents which first came into general use are still quite adequate for our everyday needs. Local anesthesia is the one outstanding addition in the past fifty years. By this I do not mean to imply that no other advances in anesthesia have been made. Rather do I wish to emphasize that, when nitrous oxide, ether, or chloroform is used with a comparable degree of modern technical skill and intelligence the results are not inferior to those secured by the use of more recently popularized drugs and methods.

I believe the present scarcity of anesthetists can almost be declared to be an emergency. To meet this acute need, I have suggested that we ought to encourage what may be called the occasional, part-time, or general practitioner anesthetist. Pursuant to that aim, the following things seem desirable.

1. We, the medical profession, ought to re-assume the responsibility regarding anesthesia which our forbears of the 19th century held and which we all but lost in the early years of this century.

2. Hospital management and the profession in general ought to encourage physicians to perfect themselves in modern methods of treat-

ing and preventing pain. Such encouragement must include both economic and professional recognition and respect. Whether such persons devote all or only a part of their time to anesthesia is immaterial. The general practitioner's diagnosis can, in a majority of cases, be quite as thorough as that of the full-time consultant in internal medicine. Similarly, the occasional or part-time anesthetist can render a service to his community which is satisfying to himself, to his fellow practitioners, and his patients.

3. Acquisition of skill through practice in administering nitrous oxide, ether, and chloroform with modern technics (free and adequate breathing, careful dosage, and the addition of oxygen) promises more for the occasional anesthetist (or for the specialist in his early training period) than does an attempt to use every new agent suggested. To get the best results from these three agents or from a simple field-block with procaine, requires the ultimate in skill of administration and management. Mastery in the use of these, I believe, should be the goal of the beginner.

4. It should be the duty of those of us who teach to see that a thorough groundwork of fundamental knowledge, and skill with the four primary agents precedes instruction in modern frills. Help for the undergraduate, for the intern, and the prospective occasional anesthetist is an integral part of our duty.

5. The aim of anesthesia is the welfare of the patient. The drugs and methods used should be within the capabilities of the anesthetist who is available. His efforts must result in a patient upon whom the surgeon can work with ease and confidence. It is my conclusion that, under the circumstances which confront us at present, the occasional anesthetist can contribute materially in bringing the maximum benefits of surgery to all of our patients.

Resection and Primary Anastomosis for Lesions of the Left Portion of the Colon

JOHN M. WAUGH¹ and MONFORD D. CUSTER, JR.²

ROCHESTER, MINNESOTA

IN DECEMBER 1945 we published an account¹ of the technic and the results of the first 50 primary resections of the left portion of the colon performed by one of the authors (Waugh). Continuity was restored in all cases by immediate aseptic end-to-end anastomosis without complementary proximal colostomy. There were 2 deaths in this series, resulting in a mortality rate of 4 per cent. The mean hospitalization period for the surviving 48 patients was 21.4 days.

The literature subsequent to the time of submission of this earlier report for publication has contained numerous excellent articles pertaining to this subject. With the notable exceptions of Lahey,² Maingot,³ and Lloyd-Davies,⁴ the majority of recent opinion frankly favors one-stage resection as opposed to the multiple-stage exteriorization type of procedure. Babcock and Bacon⁵ have expressed a preference for the former method because it is more radical as well as more generally satisfactory, and have stated they have discarded the Mikulicz-Paul technic except to terminate an operation quickly in the face of gross contamination. Wangenstein⁶ re-

ported a combined series of 139 primary resections performed without simultaneous colostomy with a mortality rate of 5 per cent. In a similar series of 20 cases reported by Meyer, Sheridan, and Kozoll⁷ from the Cook County Hospital, the mortality rate was also 5 per cent, the one death resulting from pulmonary embolism. The mortality rate in McMillan's⁸ series of 27 cases was 3.7 per cent, and in that of Clute and Kenney⁹, 6 per cent for 48 cases.

White and Amendola¹⁰ reviewed the history of resection of the colon at the Roosevelt Hospital in New York City, where exteriorization has been abandoned in recent years in favor of primary resection. In support of the latter procedure, these authors regarded it as safer than extraperitoneal resection in addition to offering the advantages of one operation, a shorter stay in a hospital, and increased resectability rate. They, however, advocated protection of the anastomosis by means of proximal colostomy or cecostomy, as did also Collier and Vaughan.¹¹ The latter authors, in discussing the problem of selection of operation, stressed the striking reduction in length of hospitalization accomplished by means of immediate anastomosis.

The British surgeons, Maingot³ and Lloyd-Davies,⁴ on the other hand, both strongly advocated the Mikulicz-Paul resection on the

¹Division of Surgery, Mayo Clinic.

²Fellow in Surgery, Mayo Foundation.

Read at the meeting of the Interstate Postgraduate Medical Association of North America, St. Louis, Missouri, October 14 to 17, 1947.

ground of increased safety. In Lloyd-Davies' series of 73 exteriorization procedures there were 3 deaths, resulting in a mortality rate of 4.1 per cent. In this country Lahey² remains the chief proponent of a staged procedure for both sides of the colon. However, he has no quarrel whatsoever with primary resection and has stated that his personal preference for the Mikulicz operation is dependent in a measure on his wide experience with it in the past. Other advantages which Lahey has emphasized are the additional safety provided by immediate decompression and the ability to examine the remaining loops of bowel with an endoscope for adjacent polyps. His operability rate for the procedure is 83 per cent and the mortality rate is 2.7 per cent, the latter figure being one which most certainly approaches an irreducible minimum for this type of surgery.

Although a difference of opinion still exists, the trend appears to favor the single-stage operation very strongly. That this approach is a sound one, surgically speaking, is borne out by the fact that substantial series of cases are now being reported in which the risk of the operation is in the neighborhood of 5 per cent. This remarkable reduction in mortality has been attributed by most surgeons to the advent of chemotherapy, although Wangenstein⁶ does not rely on the routine use of sulfonamide compounds either orally (sulfasuxidine, sulfathaladine), intraperitoneally, or parenterally.

From the pathologic standpoint additional support has been gained for segmental resection (anterior resection) of lesions so distally located within the lower portion of the sigmoid, the rectosigmoid, and the upper portion of the rectum as to preclude exteriorization. These lesions have heretofore required abdominoperineal resection, which procedure necessitates permanent sacrifice of the normal sphincter mechanism. The recent work of Glover and of one of the authors (Waugh)¹² in respect to the retrograde lymphatic spread of rectosigmoidal and rectal malignant lesions has convinced us that anterior resection of these lesions is as thoroughly curative as the more extensive Miles type of resection.



JOHN M. WAUGH

THE present report is concerned with 147 new cases. Thus the total number of cases, including the 50 previously reported, is 197, all of which operations were performed during the five-year period from January 1942 to December 1946, inclusive.

GROUPING OF CASES

In our original report we found it convenient to divide our cases into two groups in accordance with the location of the lesion in the bowel. This arrangement is again followed, since we have found a relatively constant statistical difference between these groups in regard to mortality, length of convalescence, and incidence of complications.

Group A (78 cases) comprises those lesions situated between the midtransverse and the midsigmoid colon, inclusive, for which an exteriorization procedure would otherwise have been performed. Group B (69 cases) comprises

those lesions situated in the lower part of the sigmoid, the rectosigmoid, and the upper part of the rectum for which combined abdominoperineal resection would otherwise have been performed. Figure 1 represents the distribution of these lesions.

TYPE OF PATHOLOGIC CHANGE

The types of pathologic change encountered were carcinoma of the colon, 131; sigmoidal diverticulitis, 10; tubo-ovarian abscess with involvement of sigmoid, 2; primary carcinoma of the jejunum with involvement of the transverse colon, 1; islet cell carcinoma of the pancreas necessitating removal of the distal portion of the transverse colon, 1; benign stricture, 1; inflammatory ulcer, 1.

In addition to a segmental resection of the colon in each case, the following additional resections were performed: left fallopian tube, 9; left ovary, 9; segment of jejunum, 2; segment of urinary bladder, 2; uterus, 3; leiomyoma of uterus, 2; tail of pancreas, 2; spleen, 1. Thus a total of 30 additional organs were resected in whole or part.

RESECTABILITY RATE

The resectability rate for cases in which exploration was performed for malignant lesions of the left portion of the colon situated far enough proximally to be amenable to either segmental resection and anastomosis or to extraperitoneal resection was 81.3 per cent (Table 1). This figure was derived as follows: A total of 278 malignant lesions of this type were explored during the five-year period 1942 to 1946, inclusive. Of these, 226 were resected, 176 by segmental resection with immediate end-to-end anastomosis, and an additional 50 by extraperitoneal resection. A staged procedure was elected in the latter group in nearly all instances because of inability to prepare the bowel properly owing to an obstructing lesion which was chronic in nature. The remaining 52 lesions were considered inoperable by virtue of extensive invasion of surrounding structures with or



MONFORD D. CUSTER, JR.

without hepatic metastasis. In 47 of these 52 inoperable cases, palliative colostomy operations were performed.

MORTALITY RATE

Nine of the 147 patients failed to survive the operation, giving a hospital mortality rate of 6.1 per cent. Considering the combined series of 197 cases, which includes the 50 previously reported, there were 11 deaths, giving an overall mortality rate of 5.6 per cent.

The mortality rates for group A and group B in the present series are 5.1 per cent and 7.2 per cent, respectively. The increased risk associated with resection of the lower-lying lesions is felt to be related to the technical difficulty of effecting a perfect anastomosis, with resulting failure of primary healing which occurs occasionally in such operations. Table 2 summarizes the mortality statistics.

Table 3 lists the causes of the 9 deaths. It will be noted that 5 patients died of causes (peri-

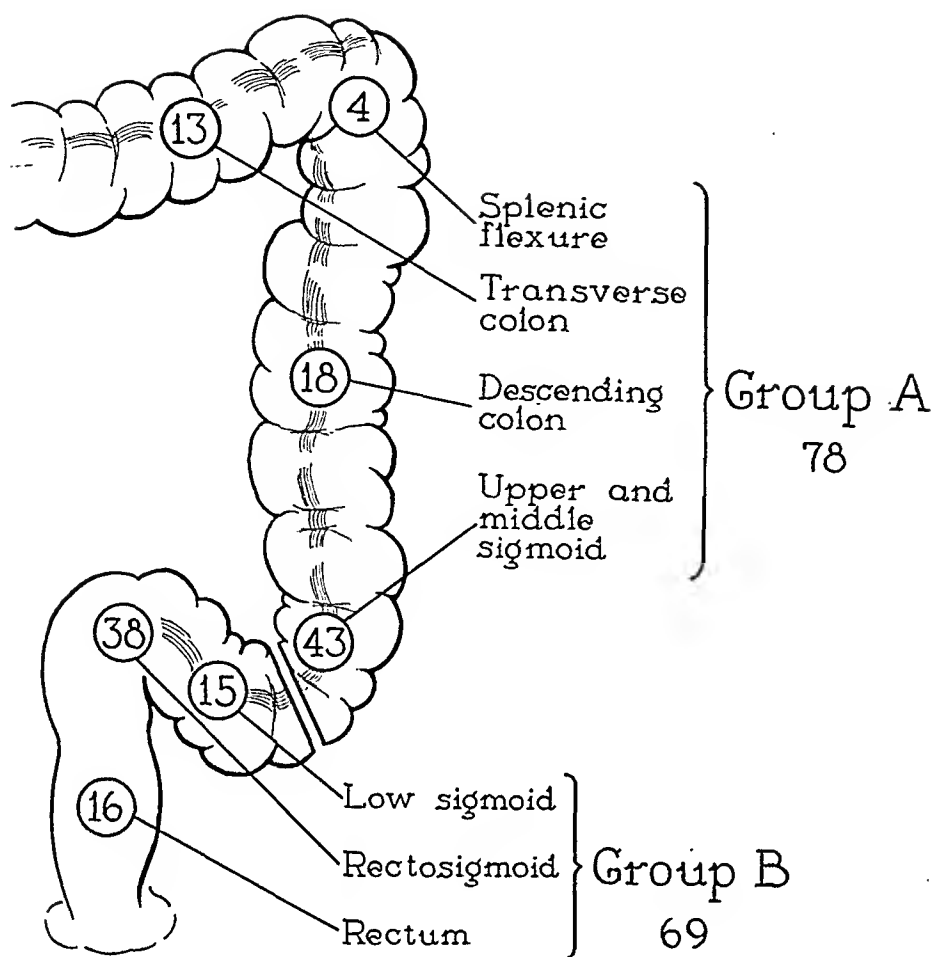


Figure 1. Site of lesions and number of cases in which lesions were at various sites in groups A and B.

tonitis or hemorrhage or both) attributable to the operation. The remaining 4 patients died of unrelated accidents. All of the latter group had postmortem examination, except the one presumably dying of renal failure.

RESECTIONS FOR MALIGNANT LESIONS

In Table 4 it is of interest to compare the hospital mortality rates of curative operations and palliative operations. The mortality rate for curative resections was less than 5 per cent, whereas the palliative resections involved a mortality rate of 20 per cent. The risk of resection of a malignant lesion was found to be slightly less than that of a benign lesion.

COLOSTOMY

We remain convinced of the fact that for resection of lesions in group A, when the bowels are unobstructed and adequately prepared, proximal colostomy is an unnecessary adjunct to the procedure. We also feel that adequate decompression is assured in the majority of resections of group B lesions by means of a 38°F. rectal tube which is passed during the operation through the anus to a point well beyond the anastomosis. However, in group B cases in which the anastomosis appears to be imperfect after its completion, it is our practice to protect the suture line further by means of a temporary complementary loop colonic stoma situated proximally. Complementary colostomy of this type

TABLE 1

RESECTABILITY RATE FOR MALIGNANT LESIONS OF LEFT PORTION OF COLON* FOR FIVE-YEAR PERIOD 1942-1946, INCLUSIVE

Operable	
Segmental resection with primary anastomosis	176
Extraperitoneal resection	50
Total resection	226
Inoperable	
Exploration without colostomy or resection	5
Palliative colostomy without resection	47
Total inoperable lesions	52
Total malignant lesions explored	278
Resectability rate for 278 consecutive cases	81.3%

*Exclusive of those treated by combined abdominoperineal resection.

was utilized in 8 of the 67 resections in group B.

It is interesting to note that simultaneously established colonic stomas were present and functioning in 3 of 6 cases in which death resulted from causes related directly to the operation. In the fourth case, death resulted from peritonitis secondary to perforation of the ileum at the site of a Witzel enterostomy that had been established after evisceration, which occurred ten days after the original operation. In the fifth case, necropsy was not permitted so that the exact condition of the anastomosis and the adjacent portion of the bowel is unknown. In only one instance did a patient without colonic stoma die of peritonitis and this patient, interestingly enough, was demonstrated at necropsy to have a concomitant bronchogenic carcinoma. Thus it is questionable in our minds whether even routine simultaneous decompression by means of colostomy would have favorably affected the mortality rate in this series (group B).

The 10 colostomies in group A were all previously performed for the following reasons: emergency decompression, 4; sigmoidovesical or sigmoidocutaneous fistula, 3; acute diverticulitis, 1; inadequate preparation of bowel at time of initial exploration, 2.

Of the 14 colonic stomas in group B, 8 were established as protective vents at the time of operation as described previously. One was es-

TABLE 2
MORTALITY RATE

	Cases	Deaths	Mortality Rate, Per Cent
Group A (new cases)	78	4	5.1
Group B (new cases)	69	5	7.2
Combined new cases	147	9	6.1
Previously reported	50	2	4.0
All cases (new and previously reported)	197	11	5.6

TABLE
CAUSE OF DEATH

	Cases
Peritonitis	4
Hemorrhage	1
Renal failure, anuria	1
Cardiac failure	1
Cerebrovascular accident	1
Unexplained	1
Total	9

established on the eighth postoperative day because of the development of a rectovaginal fistula and one for a sigmoidocutaneous fistula as a preliminary procedure. The remaining 4 had been previously established as emergency measures for acute obstruction.

PALLIATION

We are in accord with Babcock and Bacon,³ who strongly advocate palliative resection. It is our feeling that obviation of the inevitable colostomy greatly outweighs the added risk from the viewpoint of both the patient and his family. In this series, 10 resections were frankly palliative either because of hepatic metastasis or because of nodal involvement beyond the limits of resectability. Two of these patients failed to survive the operation.

COMPLICATIONS

Group A—Of the 76 survivors in this group, one had a serious complication. This patient had multiple enterocutaneous fistulas requiring re-exploration eleven months after resection. The fistulas were found to arise from a loop of ileum which had become incarcerated in a

TABLE 4
RESECTIONS

Group	Cases	Deaths	Mortality Rate, Per Cent
<i>Malignant lesions</i>			
Group A curative...	59	3	5.1
Group B curative...	63	3	4.8
Total curative	122	6	4.9
Group A palliative...	6	0	0
Group B palliative...	4	2	50.0
Total palliative	10	2	20.0
Total cases	132	8	6.1
<i>Benign lesions</i>			
Total cases	15	1	6.7

small incisional hernia. The colocolonic anastomosis was completely healed. Convalescence from this operation was uneventful.

Other complications in group A included cystitis, 3; thrombophlebitis, 2; wound infection, 1; hematoma in wound, 1; obstruction of the vesical neck, 1; drug reaction (sulfadiazine), 1.

Group B—There was a considerably higher relative incidence of complications together with a course of convalescence which was in general less smooth and more prolonged than that of the patients in group A. This is in accord both with our previous findings and with the experience of Wangenstein.⁶ The latter noted delayed healing following resection of low-lying lesions, and attributed it to vascular impairment associated with the extensive mobilization which is required from the anterior sacral space.

THREE of the 52 survivors in group B had serious complications related directly to the resection of the bowel.

1. One patient had a large abscess in the hollow of the sacrum with prolonged drainage, necessitating hospitalization for ninety-four days. This complication developed despite a well-functioning colonic stoma established at the time of resection. However, the symptoms gradually subsided with conservative treatment, and it was possible to close the stoma successfully eighteen months after the initial operation was done.

2. One patient had a rectovaginal fistula eight days after resection of a carcinoma of the rectum. Digital examination revealed the anastomosis to have partially separated. A descending loop colostomy was performed. The fistula healed spontaneously and the stoma was closed eight months later.

3. One patient had a large pelvic abscess, severe hemorrhage, and eventual separation of the anastomosis after sigmoidal resection for diverticulitis in August 1944. After a prolonged septic course, the bowel was re-anastomosed in February 1946. Convalescence was uneventful and it was possible to close the proximal stoma two months later.

Other complications occurring in group B included cystitis, 5; wound infection, 5; pelvic cellulitis, 4; transient fecal fistula closing spontaneously, 4; urinary retention (transient), 3; partial disruption of suture line healing spontaneously, 2; pulmonary embolus, 2; temporary (six months) diarrhea improving spontaneously, 2; thrombophlebitis, 2; hemorrhage, 1; parotitis, 1; transient ascites, 1; transient obstruction of the small bowel spontaneously relieved, 1.

TABLE 5
HOSPITALIZATION TIME

Group	WITHOUT COLOSTOMY		WITH COLOSTOMY	
	Cases	Ave. No. of Days	Cases	Ave. No. of Days
Group A	64	16.5	10	54.5
Group B	50	22.7	14	60.0
Total	114	19.0	24	57.4

HOSPITALIZATION

Table 5 contains figures relative to convalescence in the hospital. It will be noted that the average period of hospitalization for all surviving patients without colostomy is nineteen days. This compares favorably with the prolonged convalescence associated with either extraperitoneal or abdominoperineal resection.

It should also be noted that a longer period of hospitalization may be expected in group B

than in group A patients in accord with the known higher incidence of complications.

SUMMARY AND CONCLUSIONS

Primary aseptic anastomosis was performed in 197 consecutive cases (50 previously reported and 147 additional cases) after resection of lesions of the left portion of the colon. Eleven patients died, resulting in a mortality rate of 5.6 per cent.

For lesions of the middle part of the sigmoid and above, this operation provides a safe, curative one-stage procedure, with the hospital convalescence seldom exceeding three weeks. For lesions of the lower part of the sigmoid, the rectosigmoid, and the upper half of the rectum, this technic provides for the eradication of malignant lesions with preservation of the lower part of the rectum and the sphincter ani. The average period of convalescence in the hospital from this operation (anterior resection) is approximately one month.

The following conclusions are drawn:

1. Primary anastomosis is the procedure of choice after resection of lesions in the non-obstructed, prepared bowel.
2. Proximal colostomy is unnecessary for lesions of the middle part of the sigmoid or above, and is of questionable necessity or value for more distally situated lesions.
3. Palliative resection with immediate resto-

ration of intestinal continuity is a logical and kindly approach despite an increase of risk.

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TOXICITY OF CHEMOTHERAPEUTIC AGENTS

IN A STUDY of antibiotics and sulfonamides, Perrin Long describes the various toxic reactions of chemotherapeutic agents. Of four sulfonamides investigated, sulfadiazine is by far the least toxic, with sulfanilamide next. Sulfathiazole is the most toxic of the four drugs tested. In similar studies of antibiotics, penicillin was found to be much less toxic than streptomycin; but the toxicity of penicillin is sufficient to demand caution in its use.

Long speaks against the local use of sulfonamides and the antibiotics. He believes that the external use of these agents as dusting powders, creams, lotions, and salves is generally contraindicated, for by so using them in minor infections the patient runs the risk of becoming sensitized to a drug which later might save his life.

Newer Drugs in the Treatment of Allergic Diseases

SAMUEL M. FEINBERG*

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO

THE average physician is frequently confused by the large array of drugs introduced in the last decade for treating allergic disease. And then if to all these drugs are added those still in use from an earlier period, his confusion increases. Some of these remedies are valuable, many are worthless, while others have limited value. Unjust advertising claims and uncritical medical articles add further to this bewilderment. These reasons prompt the presentation of an evaluation of some of these drugs.

SYMPATHOMIMETIC OR VASOCONSTRICTING DRUGS

Epinephrine is still a very useful drug in the temporary relief of allergic manifestations. In addition to the customary use of hypodermic injections of epinephrine 1:1000, inhalations of epinephrine solution of 1:100 are now commonly employed for self-medication in asthma. Several manufacturers have marketed stronger solutions and have sold them under trade names directly to the patient.

Inhalations of epinephrine are useful in mod-

erate attacks of asthma and have the advantage of being relatively free from systemic effects and of permitting the patient to use effective medication early in the attack. However, if used to excess or indiscriminately such medication may do considerable harm. It is therefore essential that it be employed only under direction of the physician.

Another epinephrine product introduced in recent years is a slowly absorbing, injectable preparation intended to prolong the duration of action of the drug. My experience indicates that such preparations do not produce the desired effect consistently; sometimes they are too slow to do any good, while at other times they are so rapid that the large dose of the drug produces violent reactions. This clinical experience has been amplified by pharmacologic experiments on animals.

Various modifications of ephedrine and drugs having ephedrine-like action have been introduced in recent years for oral use. Racephedrine (d-l-ephedrine) is somewhat less potent and less toxic than natural ephedrine, and may be used often as a substitute when the latter is not tolerated. Propadrine hydrochloride (diphenyl-l-amino-2-propanol-1-hydrochloride), in doses of $\frac{3}{8}$ to $\frac{3}{4}$ gr. (25 to 50 mg.), is a useful drug for those who obtain too much excitation

*From the Department of Internal Medicine, Division of Allergy, Northwestern University Medical School.

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from ephedrine; however, it is not as constantly effective as ephedrine.

Many commercial ephedrine products differ only in the nature of the sedative added to counteract the stimulating effect of ephedrine. The combination of choice should depend on the degree and duration of the sedation desired, the individual patient's behavior, and some other circumstances.

For topical use as nasal vasoconstrictors, a number of medicaments have been added to the old list of ephedrine products. A very popular form is the benzedrine inhaler. If not used too frequently it is a valuable vasoconstrictor in many instances. Tuamine solutions and inhalers have been marketed in recent years. Among the topical vasoconstrictors which are milder than ephedrine are paredrine hydrobromide, 1 per cent, propadrine hydrochloride, 1 to 3 per cent, and racephedrine hydrochloride, 1 per cent. Two products in particular are more potent than ephedrine: Neosynephrine hydrochloride is usually employed in $\frac{1}{4}$ per cent strength and occasionally in 1 per cent concentration in obstinate cases. Privine hydrochloride is the most potent of all and is marketed in strengths of $\frac{1}{20}$ per cent (0.05 per cent) and $\frac{1}{10}$ per cent (0.1 per cent).

The disadvantage of very potent vasoconstrictors is that the local ischemia they produce may be so complete that when the effect wears off there results a compensatory vasodilatation. This "rebound" congestion calls for further use of vasoconstrictors. Thus a vicious cycle may result in which the congestion is maintained because of the use of drops. Our experience has made us loath to employ any strong topical remedies in allergic patients, unless intended only for occasional use. Recently I have found that satisfactory shrinking effects could be obtained with Privine solutions of 0.03 per cent or 0.02 per cent, with much less of rebound penalty.

THERE is an increasing tendency for addition of antiseptics, sulfonamides or antibiotic drugs to vasoconstrictors. The average allergic



SAMUEL M. FEINBERG

nose neither needs nor tolerates antiseptics well. The promiscuous use of penicillin, sulfonamides, and similar drugs in conditions where they are not needed may eventuate into an induced sensitivity which could interfere with the use of such drug when the need is desperate.

ANTIBIOTIC THERAPY

Since bronchial infection is an accepted cause of a large group of asthma cases it is natural the modern bacteriocidal substances should be tried for them. Several workers have claimed varying degrees of success with sulfonamides. Applebaum employed sulfathiazole aerosols and claimed improvement in 86 per cent of the patients treated.

Schonwald and Deppe were the first to report on the use of penicillin in a large series of asthma cases. They gave injections of rather small doses and claimed excellent results. The results of Hampton and his associates as well as those of Leopold and Cooke were moder-

ately favorable. Barach and his co-workers obtained encouraging results by using penicillin aerosols; Vermilye gave an enthusiastic account of efficacy of penicillin aerosols in asthma.

My experience is that penicillin aerosol therapy is helpful in some cases of infectious asthma. It is, of course, of no help in the ordinary allergic case. Since there are many patients with asthma whose allergic causes cannot be identified and which are nevertheless neither intrinsic nor bacterial, it stands to reason that a large proportion of this group will not respond to penicillin. Although more lasting results may be obtained in some cases of infectious asthma, in most instances the effects of penicillin treatment are apt to be temporary. The more chronic and more complicated the asthma the less likely is it apt to be influenced materially by penicillin. When special apparatus for the administration of penicillin aerosols is not practicable the patient may use an ordinary hand nebulizer, aerosolizing about one-half cc. of a solution containing 20,000 units of the drug, every three hours.

Although allergic reactions to penicillin are quite common there is no evidence that the asthmatic group is more prone to such reactions. It is possible that streptomycin therapy may be helpful either alone or combined with penicillin in certain types of asthma. Allergic reactions to streptomycin must also be considered, since Keefer and his associates have reported an incidence of about 5 per cent of skin rashes following streptomycin administration.

VITAMINS

Practically all known vitamins have had their advocates in the treatment of allergic disease. The favorable claims for vitamin D, particularly with large doses (60,000 to 300,000 I.U.), have not been substantiated. Vitamin A has been of no help, either alone or added to D. Thiamin has not been effective and the claims for lactoflavin have not been corroborated. Nicotinic acid and nicotinamide offer no benefit, although the vasodilating effects of nicotinic acid, particularly parenterally, may

have at times a desirable but temporary pharmacologic effect.

Vitamin E was found to be of no value in allergy. The claims for inhibition of anaphylaxis and sensitization to chemicals by vitamin P have not been confirmed. The good results reported with vitamin K in urticaria by one worker have not been possible to duplicate in my practice nor in that of my colleagues.

Vitamin C has probably been the most frequently used vitamin in allergy. The claims of Hagiesco and his associates for the effectiveness of intravenous injections of vitamin C in asthma were negated by subsequent workers. The enthusiastic report of Holmes and Alexander in 1942 was largely responsible for the widespread use of ascorbic acid in hay fever and other allergic conditions. Hebard and Englesher reported that their results with this vitamin were poor. Friedlaender and I showed that hay fever subjects had a normal blood level of vitamin C and that large doses of the vitamin produced the usual saturation blood levels but had no effect on the course of the hay fever or asthma. In spite of these reports and others and the almost unanimous opinion of allergists that vitamin C is of no benefit in allergic conditions, it still continues to be a form of self-medication by many hay fever sufferers.

HORMONES

Endocrine disturbances are no more common in allergic people than in the general population, and when they are present they are usually neither the causes nor the results of the allergy. Of course, any profound metabolic alteration may aggravate an existing allergy. Thus, a hyperthyroidism may upset the nervous system sufficiently to make an asthma worse. Hypothyroidism rarely has the same effect. If hypothyroidism exists thyroid medication is indicated, but rarely will it result in improvement of the allergy. Parathyroid, spleen or liver extracts, advocated at one time or another as remedies for allergic disease, may be regarded as devoid of any particular merit, except for the slight nonspecific effects that may occur from their injection.

Cortical extract of the suprarenal gland, at first advocated in the treatment of allergic disease, has been finally judged lacking in effectiveness. Desoxycorticosterone has not been helpful, and the claims for the efficacy of oral administration of a concentrate of the entire suprarenal gland have not been confirmed.

It is common experience that allergic manifestations are apt to be influenced by the cyclic changes in the physiology of sex hormones. The frequent aggravation of allergic symptoms in the premenstrual phase, the improvement in allergic manifestations often occurring during pregnancy, and the changes in allergic status in one direction or another sometimes occurring at puberty or menopause, are accepted phenomena.

Several explanations for these observations have been offered. Some are of the opinion that these manifestations may represent an allergy to a hormone. Others believe that hormones may play a specific role in the production of allergy. The most likely explanation, however, is that endocrine disturbances, like other secondary causes, may act in a nonspecific manner by upsetting the allergic equilibrium. Theelin and other sex hormones have had very little effect in such cases. On the basis of Zondek's claims I have been able to suspect at times an autogenous allergy to estrogenic hormones and have been successful in a few instances in relieving allergic symptoms by giving desensitizing injections of the hormone.

MINERALS AND ACIDS

Since there is no calcium deficiency in allergy and since large doses of calcium salts orally do not modify capillary permeability, there is very little indication for the use of calcium in allergic patients. Occasionally urticarial lesions are benefited temporarily by intravenous injections of calcium salts. Potassium chloride still continues to be sold over the counter and is warmly recommended by some medical columnists, although the evidence is conclusive that it is of almost no value in allergy.

Phosphorus compounds had a temporary

vogue because of an alleged phosphorus deficiency in allergy; this deficiency was subsequently disproved by carefully conducted laboratory tests. Hydrochloric and nitrohydrochloric acids have had their day as specific remedies for hay fever; it is now generally conceded that acids are only of occasional help in food allergy insofar as they might at times improve digestion.

Arsenic, an old remedy for asthma mentioned in text books of the nineteenth century, has recently had a revival of interest. Arsenic helps only a small percentage of the sufferers, although it not infrequently aids the general condition by improving appetite and perhaps other functions. It must be remembered, however, that long continued and unsupervised arsenic medication may produce serious toxic effects.

MISCELLANEOUS REMEDIES

Anoxemia is not present in the usual asthma attack and oxygen is therefore not ordinarily indicated. In status asthmaticus or in a very acute asthma attack with cyanosis oxygen may be helpful. The use of inhalation mixtures of 80 per cent helium and 20 per cent oxygen is of considerable aid in persistent asthmatic states. Inhalation of 5 to 8 per cent carbon dioxide may be helpful in promoting expectoration and in increasing the cough reflex in status asthmaticus and in atelectasis.

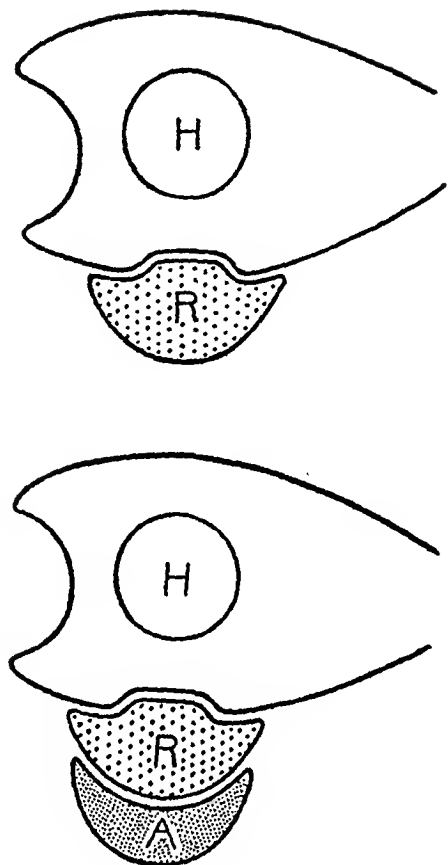
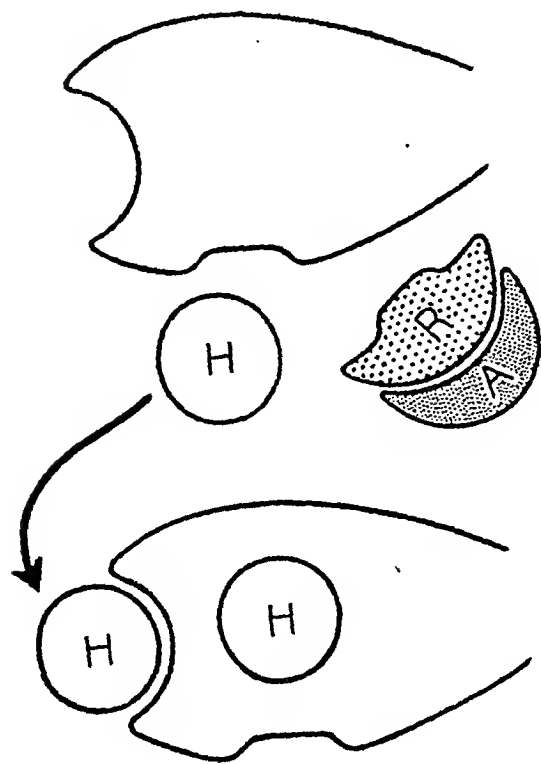
Demerol, at first considered a very useful drug in asthma because of its antispasmodic and hypnotic actions, is now regarded by most observers as not much different from morphine in its disadvantages. Its objections are that it suppresses the cough reflex, it may be habit forming, and its effectiveness in asthma is not marked. Procaine intravenously has been recently advocated in serum sickness and urticaria. Since procaine allergy is not rare, it must be emphasized that such therapy can be distinctly dangerous.

Ethylene disulphonate, claimed by the manufacturer to be very effective in allergic disease, has been found without demonstrable virtue.

HISTAMINE RELEASE MECHANISM IN ALLERGY

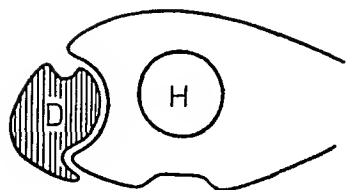
Sensitized cell. Allergic cell has attached sensitizing antibodies—*reagins* (R). All cells, allergic or not, have *histamine* or its precursor (H) which causes no harm while within the cell.

Antigen-reagin union. *Antigen* (A) unites with *reagin* (R) on the sensitized cell.



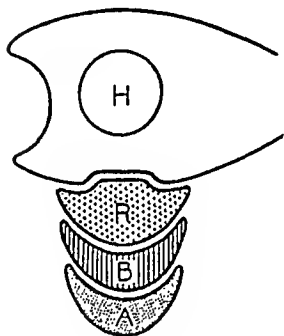
Release and action of histamine. Union of *antigen* and *reagin* causes release of *histamine* from within sensitized cell. This histamine is free to attach to receptors on adjacent cells, causing damage which results in allergic symptoms.

Figure 1



CONCEPT OF VARIOUS METHODS USED TO COMBAT HISTAMINE

Desensitization produces immune or *blocking antibody* (B) which attaches to reagin and prevents union of reagin and antigen.



Chemical block. Benadryl, pyribenzamine, neo-antergan, and similar drugs (D)* attach to histamine receptors, thus blocking attachment of released histamine.

Figure 2

SYMPTOMATIC THERAPY OF HISTAMINE EFFECTS

Edema—corrected by: Epinephrine, ephedrine, and other sympathomimetics.

Smooth muscle spasm—corrected by: Aminophylline, epinephrine, nitrites, stramonium, caffeine.

Mucous gland dysfunction—corrected by: Iodides.

Excitation—corrected by: Sedatives.

*Note that the chemical block (D) has not the identical structure of histamine accounting for some of the additional effects from the antihistaminic drug.

Archibald showed that this drug intramuscularly was no more effective than injections of distilled water, both producing a slight non-specific improvement in an occasional patient. Experimental and clinical data indicate that this substance is not antianaphylactic nor anti-allergic. The Council on Pharmacy and Chem-

istry of the American Medical Association states that the existence of such a compound is open to serious doubt. It says further that "the theory of its dilution and its supposed part as an oxidative catalyst of carbohydrate metabolism is based on flimsy biochemical conjectures that have no proved connection with the mecha-

ism of allergy." The claimed dilution of 1^{10-15} is equivalent to 1 mg. of the substance in 250,000,000 gallons of water. At the prevailing price of the ampule 1 mg. of the chemical would be worth 5,000 billion dollars. Reports of favorable results are based on observations not eliminating the likely possibilities of spontaneous remissions, nonspecific effects of injecting distilled water, and psychogenic influence.

Anthallan is another alleged antiallergic remedy which created temporary excitement as a result of publicity given to a clinical report which lacked many of the features of controlled observation. The experience of a number of specialists in allergy indicates that this drug is of no value in allergic conditions. Furthermore, in preliminary experiments I have found that this drug has essentially no antihistaminic nor antianaphylactic properties.

Recently it has been reported that irradiation of the nasopharynx with the radium applicator was helpful in the treatment of the asthmatic child who had residual lymphoid tissue in the nasopharynx. This claim awaits confirmation.

POSSIBLE METHODS OF COMBATING HISTAMINE

Since Dale and Laidlaw in 1910 pointed out the similarity between manifestations of histamine shock and anaphylaxis in animals, and Lewis and Grant in 1926 called attention to the similarity between allergic and histamine wheals in man, considerable evidence has accumulated indicating the importance of the role of histamine in the mechanism of the allergic manifestations. It must be emphasized that although histamine release is regarded as an important part of this mechanism, there is increasing evidence that additional activities are also at play.

The mechanism of histamine release generally conceived is as follows: Histamine, or its precursor, resides within the cell, more in some tissues than in others. As long as histamine is not released from the cell it does not injure that cell or adjacent cells. The union of the antigen (such as pollen) with the reagin anti-

body on the cell of the allergic person results in a liberation of histamine (Figure 1). The latter not only injures that particular cell but also neighboring cells, and if the amount of histamine is sufficient it may affect remote tissues. Some of the known results of such histamine effects are contraction of involuntary muscle, increased capillary permeability, and stimulation of secretion of some of the excretory glands.

How, then, can we combat this histamine action? (Figure 2).

1. *By preventing the union of antigen and reagin.* The method long available is the process of desensitization by repeated and increasing injections of the specific antigen. It has been shown that such a procedure produces a new substance, the blocking antibody, which prevents the union of antigen and reagin. With the failure of this union no injury to the cell results and no histamine is released. The disadvantages of this method are, of course, the long continued treatment required and the fact that not all of the union of antigen and reagin can be blocked under all circumstances. It is possible that more perfect methods will be evolved to accomplish this effect, and perhaps other means than specific desensitization may be discovered to prevent the union of antigen and reagin.

2. *By increasing the tolerance to histamine.* This is theoretically possible by at least two mechanisms: (1) a general increase in resistance of the cells to chemical injury, including that due to histamine, and (2) a specific increase in histamine tolerance. It is well known that there is a variation in tolerance to histamine in different persons and in individuals of the same species of laboratory animal. It is not known, however, what constitutes the nature of this variation.

Attempts to increase histamine tolerance by specific immunization have not been successful. Although histamine injections have been and still are widely employed in allergic conditions there is no evidence that tolerance to histamine is built up in this manner. In the experimental animal, too, the preponderance of evidence

indicates that tolerance to histamine cannot be produced by subjecting the animal to repeated doses of the chemical, although temporary refractoriness may thus result. Furthermore, there is no basis for belief that allergic manifestations are produced because of a heightened sensitivity to histamine, and that proposed tests with histamine to classify people as allergic are fallacious.

IN SPITE of all these considerations, it is possible histamine treatment may occasionally produce beneficial effects. It may possibly help in some instances of urticaria and cold allergy. Whatever good results are obtained must be explained on a basis other than desensitization to histamine.

Since histamine is a simple chemical substance and could not ordinarily be expected to produce antibodies for increased tolerance it was thought that by conjugating it to a large molecule, such as a protein, immunization to it could be made successful. The claims for this histamine-azo-protein were that it produced antibodies specific for the histamine portion of the conjugate in animals and in man, that it increased the tolerance to histamine and that it was effective in the treatment of allergic manifestations. Most critical experimenters and observers agree that there is no evidence that this substance increases the tolerance to histamine or that it has a specific antianaphylactic or antiallergic effect.

My own experience indicates that histamine-azo-protein does not have a high incidence of effectiveness in the treatment of allergic conditions, and when it does occasionally produce benefit it is probably due to the non-specific action of the foreign protein. Incidentally, it is important to call attention to the fact that the despeciated horse serum globulin which is part of the molecule of the histamine-azo-protein is still capable of producing severe allergic reactions in those who are sensitive to horse serum.

Another means of increasing the resistance of the cells to histamine is by competitive attachment of a less toxic chemical to the cell

receptors available for histamine. This is regarded as the mode of action of the so-called histaminic antagonists, benadryl, pyribenzamine, neoantergan, and similar drugs, as well as the amino acids, histidine, cysteine and arginine. These antihistaminic drugs will be discussed more fully in the last portion of the paper.

3. *By destroying the liberated histamine.* Since the discovery in 1929 by Best that some of the tissues contain an enzyme which is capable of destroying histamine, numerous efforts have been made to establish this enzyme histaminase as a therapeutic drug. The early claims of antianaphylactic and antiallergic action of this substance have been denied by later more critical experimental and clinical evaluations. It is true that histaminase when incubated with histamine for several hours will destroy moderate amounts of the latter. However, the conditions under which this drug would have to work in the living animal are apparently not the same. It has been concluded by the original discoverer of histaminase as well as by the Council on Pharmacy and Chemistry of the American Medical Association that there is no basis for its therapeutic use.

4. *By counteracting the effects of histamine.* Some of the known effects of histamine can be remedied by drugs having specific pharmacologic action. Vasodilating effects of histamine can be in large part corrected by various sympathomimetic or vasoconstrictor drugs such as ephedrine and epinephrine. Aminophylline and similar drugs relax the smooth muscle spasm and are most useful in asthma. Aminophylline orally is least effective, but is more useful when used in combination with ephedrine. Aminophylline intravenously (3- $\frac{3}{4}$ to 7- $\frac{1}{2}$ gr.) is highly efficacious in many attacks of asthma. When intravenous medication is not practicable quite good results are frequently possible from the use of aminophylline suppositories (5 to 7- $\frac{1}{2}$ gr.).

Recently it has been claimed that aerosols of aminophylline solution are effective in some cases of asthma which do not respond to intravenous aminophylline. It should be remembered that aminophylline may be more helpful

in one stage (bronchospasm) of asthma while the vasoconstrictor drugs may be more effective in another stage (edema of the mucosa).

Among other effects of histamine action is the stimulation of secretory glands. Part of the respiratory discomfort in asthma is a result of bronchiolar obstruction by the tenacious mucus. The iodides constitute the ideal drugs in ameliorating that effect by stimulating the glands to produce a thin secretion.

NEW HISTAMINE ANTAGONISTS

Substances having a competitive action with histamine have been sought for a long time. The amino acids histidine, cysteine and arginine, were found to be antihistaminic and anti-anaphylactic, but the toxicity of the large doses necessary for these effects precluded their use. In France, long continued systematic attempts to produce synthetic antihistaminic compounds finally resulted in the clinically useful drug antergan (N'-phenyl-N'-benzyl-N-dimethylethylenediamine), which was later replaced by the less toxic neoantergan (N-p-methoxybenzyl-N-dimethylaminoethyl- α -aminopyridine). In Europe the latter is now the representative drug of the histamine antagonists. I have found neoantergan, which has been at my disposal for more than two years,* an active drug experimentally and clinically.

The antihistaminic drugs in present use in this country are benadryl (B-dimethylaminoethyl benzohydril ether) and pyribenzamine (N'-pyridyl-N'-benzyl-N-dimethylethylenediamine). Their action has been discussed in considerable detail in many papers. Here I wish only to summarize their uses and limitations. In a large percentage of hay fever patients they are effective in the symptomatic relief of many of the symptoms, pyribenzamine being more consistent in its action. The hyperesthetic symptoms (sneezing and itching) are more often relieved than the edema (blocking). The symptoms early in the season, those in the milder cases and those occurring in patients who have had specific desensitization are more often benefited.

In the perennial allergic or vasomotor rhinitis, the incidence and degree of relief are not as great as in the seasonal; here, too, pyribenzamine has an advantage over benadryl. The dyspnea of asthma is not appreciably relieved by either of these drugs, although the spasmodic cough of the early stage of asthma may respond well. Now and then I have found that the combination of pyribenzamine with ephedrine or aminophylline or both produces an effective synergistic remedy in asthma.

Both drugs have a high incidence of effectiveness in the relief of the symptoms of urticaria, angioneurotic edema, drug rashes, dermatographism, and the delayed "serum sickness" occurring after the administration of serum, penicillin or sulfonamides. The itching is benefited most, although the edema is usually also reduced and held in abeyance. When joint symptoms are present they are the manifestations most resistant to this therapy. In all of these patients it is necessary to give the drug frequently, usually every four to six hours, since its discontinuance results in a recurrence of the manifestations. There is no reason to believe that the duration of the disease is shortened by these drugs.

In eczema (atopic dermatitis) benadryl and pyribenzamine have been found effective in relieving itching in a large percentage of cases. In a few instances the prevention of the trauma from the cessation of the scratching favors the resolution of the dermatitis. Sometimes the itching of other conditions, such as pruritus ani, pruritus vulvae, and contact dermatitis and dermatomyositis, is also helped.

In patients having difficulty in avoiding constitutional reactions from desensitizing injections of antigen, I have found that the administration of pyribenzamine or other effective antihistaminic drug thirty to sixty minutes prior to the injection helped to diminish the intensity and the likelihood of a reaction. It should be emphasized that such inhibiting action is only moderately quantitative, that it does not always work, and that one can obtain reactions if the dose of the antigen is excessive. The discomfort, and particularly the itching, occurring

*First supplied to me through the kindness of Dr. B. N. Halpern and the Rhone-Poulenc Laboratories, Paris, France.

locally from the antigen injection in some instances may also be improved with these drugs. A dose of the histamine antagonist may also be helpful when one is compelled to subject himself to a known allergenic contact, such as a specific food or a dog. Other conditions in which these drugs may be useful at times are gastrointestinal allergy and allergic headache.

These drugs are usually given orally in 50 mg. doses to the adult. Pyribenzamine as a rule is tolerated in higher doses, and where needed can be frequently administered in 100 to 150 mg. amounts. Infants require 10 to 20 mg. of pyribenzamine, young children require 25 to 50 mg. doses, while older children tolerate and require adult doses. It is peculiar that not infrequently the child will tolerate the drug better than the adult. For young children or when small doses are used the drug may be taken dissolved in a sweetened vehicle. Because of the sedative action of these drugs it may be advisable at times to combine them with stimulants—ephedrine, amphetamine, or caffeine.

In special instances either drug may be given intramuscularly or intravenously in doses considerably smaller than those used orally. I have found that in some asthmatic patients an aerosol of pyribenzamine is effective in relieving the cough and dyspnea. In itching dermatoses, especially in eczema and in pruritus ani, I have utilized an ointment in which the pyribenzamine was incorporated. This has been of additional help with some patients who had partial relief from oral administration and has helped others who have not had much relief from the ingested drug.

The side actions of these drugs are not inconsequential. This is particularly true of benadryl which causes sleepiness in 50 per cent of the patients in many of whom it is of sufficient degree to make the use of medication inadvisable. Pyribenzamine also causes sedation, but does so less often and less intensively. Other effects which may be objectionable are dizziness, lassitude, disturbance in power of concentration, palpitation, fall in blood pressure, nervousness, insomnia, gastric irritation, and diarrhea. A dryness of the mouth and throat

is not an infrequent complaint. Mental alertness is frequently diminished and it is important, therefore, to caution the patient about its use, particularly during his active hours.

In addition to benadryl, pyribenzamine and neoantergan we have been using experimentally and clinically several other drugs having similar actions. This is not the place to report in detail on these new drugs. A general statement, however, may not be amiss. Some of these drugs have an advantage over those on the market in that they are less toxic; others, although not having as high an efficiency index as pyribenzamine, are nevertheless the most effective drug for particular individuals; while still others are too toxic.

It is possible that further experience may show that some of these drugs are more useful in particular allergic manifestations. Some have promise of advantage because of longer duration of action. It is possible that drugs having additional activity other than antihistamine action may be developed; these may possibly be more effective in allergy.

There is considerable misunderstanding about the use of the antihistaminic drugs. Since their action is almost immediate it is not necessary to give these drugs for long periods to determine their effectiveness. If the drug is effective it can only help for a number of hours and must be repeated frequently. These drugs do not help all types of allergic manifestations nor all patients with any particular type of allergy. Neither are they effective to the extent of eliminating all symptoms of an allergic attack. They do not replace the more lasting benefit obtainable by successful specific avoidance or desensitization. Their toxic side actions frequently make them objectionable.*

*Two or three additional new drugs with which I have had considerable experience and which may be marketed soon, are worth mentioning here. Antistine (2-(N-phenyl-N'-benzyl-aminomethyl-imidazoline), marketed in Europe, is only moderate in its antiallergic effects, but is relatively free from undesirable side effects. Thenzlene or histadyl (N-(2-pyridyl)-N'-(2-thienyl)-N'-dimethylethylenediamine), and chlorothien (N, N'-dimethyl-N'-(2-pyridyl)-N'-(5-chloro-2-thienyl)-ethylenediamine) are potent antihistaminic and allergic drugs.

The Acute Abdomen

ROENTGENOGRAPHIC AIDS IN DIAGNOSIS

LEROY SANTE*

ST. LOUIS UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS

THE WORD abdomen means "hidden" and indeed it seems quite appropriate since the diseased conditions of the abdomen are often baffling. Many diseases of the abdominal organs become chronic and can be investigated at leisure, but not infrequently abdominal conditions arise which require prompt diagnosis and immediate treatment. Roentgen examination offers a means by which such conditions often may be detected.

We have found four positions most valuable for the roentgenographic survey examination of the abdomen:

1. Anterior view of the chest, with the patient in the upright position. This examination is especially valuable for the detection of free gas below the diaphragm.

2. If the patient is too sick to assume the upright position, an anterior view of the abdomen may be made with the patient lying on the left side. This view serves especially well to show free gas in the abdomen and fluid levels in the hollow viscera. The right flank shadow may show exceptionally well and gas-distended loops of intestine are floated upward upon any exudate which may be present.

3. Anterior film of the abdomen with the patient in a prone position serves as a survey film to observe the size, form, and location of the

abdominal organs, gaseous distended loops of bowel, fecal impaction, and biliary or urinary calculi. It also affords a good view of the flank shadows on either side of the abdomen.

4. A transabdominal view of the abdomen, with the patient lying on his back and the x-ray beam projected horizontally across the abdomen from side to side. This view gives the best impression of any abdominal exudate.

All of these views must be included in the examination in order that no vital information is overlooked. This technic alone often provides the information necessary for a correct conclusion as to the underlying pathology.

Rupture of a hollow viscus such as stomach or duodenum from peptic ulcer or of the small bowel from injury allows gas in the viscus to escape into the abdomen. It may be assumed that any gas free in the abdominal cavity is from this source. Gas rises to the top so that it will be found in the roentgenogram in a small collection under the diaphragm with the patient in an upright position. With the patient lying on the left side it will be found between the liver and lateral abdominal wall. When present, these findings may be considered as absolute indication of rupture of a hollow viscus. This sign is positive in 80 per cent of ruptured peptic ulcers; it is invariably present in ruptured typhoid ulcers of the small bowel. Prompt diagnosis of rupture of a hollow viscus is of utmost importance since the mortality of operative procedure rises markedly after the first few hours.

*Professor of Radiology and Director of the Department, St. Louis University School of Medicine, St. Louis.

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Many abdominal conditions are associated with gaseous distention of the intestines. Some of the conditions most frequently encountered in which dilatation is a prominent factor are:

(1) Intestinal obstruction (complete), (2) paralytic ileus (generalized), (3) localized paralytic ileus (due to infection or irritation), (4) localized spastic ileus, and (5) mesenteric thrombosis—arterial, venous.

INTESTINAL OBSTRUCTION

When complete mechanical obstruction of the bowel occurs, vigorous peristalsis develops in an effort to overcome the obstruction. This involves the entire bowel both above and below the site of obstruction and is attendant with paroxysmal colic. Later these attacks subside and there is almost complete absence of any painful manifestation. Peristalsis empties the segment of the bowel below the obstruction, so that it is possible to have a bowel movement after obstruction has taken place. Once rid of its contents the distal segment of the bowel becomes flaccid and remains so; the rectum should be free from gas. The portion proximal to the obstruction, however, unable to rid itself of its contents, rapidly fills with gas.

WHERE the gas comes from, and the mechanism by which it forms, is not fully understood, but in all probability its chief source is from the products of putrefaction, and from interference with absorption by the blood stream. Roentgenologically, these gas-filled loops of bowel take on a characteristic appearance. By reason of its extreme dilatation the small bowel shows accentuation of the valvulae conniventes, giving rise to the so-called "herringbone" design. The loops of bowel arrange themselves back and forth across the abdomen forming a "stepladder" pattern, which is quite characteristic of the condition. These findings are best demonstrated in the anterior prone view of the abdomen.

Within a few hours after obstruction fluid is excreted into the bowel, giving rise to the roentgen sign of multiple fluid levels. This is due to



LEROY SANTE

partial interference with the blood supply squeezing the blood vessels between the intestinal coats. Large amounts of intestinal fluid are repelled back into the stomach by reverse peristalsis in an effort to rid the body of this toxic material and vomiting then begins in earnest. This culminates in fecal vomiting which is definite evidence of complete obstruction. Toxicity may become so great that the patient no longer feels sick but attains a deceptive feeling of well being. Continuous aspiration of stomach contents with Wangenstein suction apparatus may so eliminate both vomiting and toxicity as to mask the symptoms of the disease. Fluid excreted into the gas-filled bowel can be detected most readily as fluid levels in the upright, lateral decubitus and transabdominal positions. It occurs most extensively in obstruction but also may be present in paralytic ileus.

At times, the small bowel is so greatly distended that it may resemble the colon, and since it is very important to determine the exact location of the gas-distended bowel, barium enema



Figure 1. Air under diaphragm from rupture of a duodenal ulcer. This is a definite indication of rupture of a hollow viscus; it is a simple procedure, very accurate in its diagnostic significance, permitting early operative repair.

may be done to identify the involved portions. In small intestinal obstruction the flaccid condition of the large bowel will readily be noted on administering a barium enema. The calibre of the colon at first is very small, but as more of the barium enema is administered it will enlarge to its natural size. There is no danger to be expected from a carefully given barium enema and the information obtained is often decisive. At times it may even give evidence of the cause of the obstruction. After the examination is completed the barium enema may be siphoned off, often leaving in the colon only a negligible amount of barium mixture which should hardly interfere in any operative procedure.

The farther down the obstruction occurs in the gastrointestinal tract the less acute are the symptoms, so that complete obstruction from carcinoma may exist low down in the colon for many days without alarming symptoms. When the colon does become distended, as from volvulus, its enlargement is enormous. Volvulus of the large bowel is prone to occur in the sigmoid region due to redundancy of the sigmoid colon.

The presence of a palpable abdominal mass associated with the roentgen manifestation of obstruction always suggests the possibility of

the mass as a cause of the obstruction. Constriction of the lumen of the bowel by a tumor mass may be converted into complete obstruction by impacted fecal material, and the mottled appearance of gas admixed with feces is quite characteristic. Barium enema examination will disclose whether the mass arises from the colon; if it arises from the small bowel it cannot be demonstrated in this manner.

It will be noted that the most outstanding symptoms of intestinal obstruction are: abdominal distention which is usually mild; vomiting which may be extensive or very mild, but it may be relied upon that vomiting should occur to some degree if obstruction is present. If fecal vomiting occurs it is in itself definite evidence of obstruction. Continuous Wangenstein drainage should not be instituted until the diagnosis is made since it may modify the clinical and roentgenographic picture and obscure the diagnosis. Pain at the outset may be intermittent and colicky in type, but never so severe or prolonged as to produce shock.

Since most obstructions encountered by the



Figure 2 (left). Complete small intestinal obstruction following operative procedure. Note gas-filled loops of bowel but no gas in large bowel or rectum. (Right) Paralytic ileus; gas distributed throughout entire bowel, both large and small.

radiologist result from postoperative adhesions, the history of previous operation is of importance. In uncomplicated obstruction there is little, if any, fever.

PARALYTIC ILEUS

In generalized paralytic ileus due to nervous inhibition from peritoneal irritation or pleural involvement, the gaseous distention involves both the small and large bowel alike. The gas-filled loops of bowel do not show the same characteristic pattern or arrangement, but give a more redundant appearance leaving their impression on each other at their points of contact. The entire colon is filled with gas, and the rectum is greatly distended.

In intestinal obstruction, on the contrary, the distal portion of the bowel is empty and flaccid and the rectum does not contain gas. This is a point upon which the differential diagnosis between these conditions depends. Incidentally, this is likewise a good clinical point; in a complete intestinal obstruction the examining finger

introduced into the rectum encounters an empty flaccid rectal pouch and the rectal mucosa falls limply about the examining finger, whereas in paralytic ileus the rectum is dilated with gas.

If paralytic ileus is caused by peritoneal infection, abdominal exudate will be present between the intestinal loops. This is best seen on the transabdominal view. If the process is an infiltrative one the lateral abdominal walls may be obscured and detail in the muscular structure may be lost.

The most outstanding clinical symptom in uncomplicated paralytic ileus is the pronounced abdominal distention; nausea and vomiting are usually entirely absent, and pain is not severe but is more in the nature of discomfort from gaseous distention. Vomiting is not a prominent symptom and is never fecal. Constipation is obstinate from the outset but fecal material may be syphoned off with an enema. In uncomplicated cases fever is not present, but if the condition is caused by or complicated with peritonitis, fever and other signs of infection will be present.

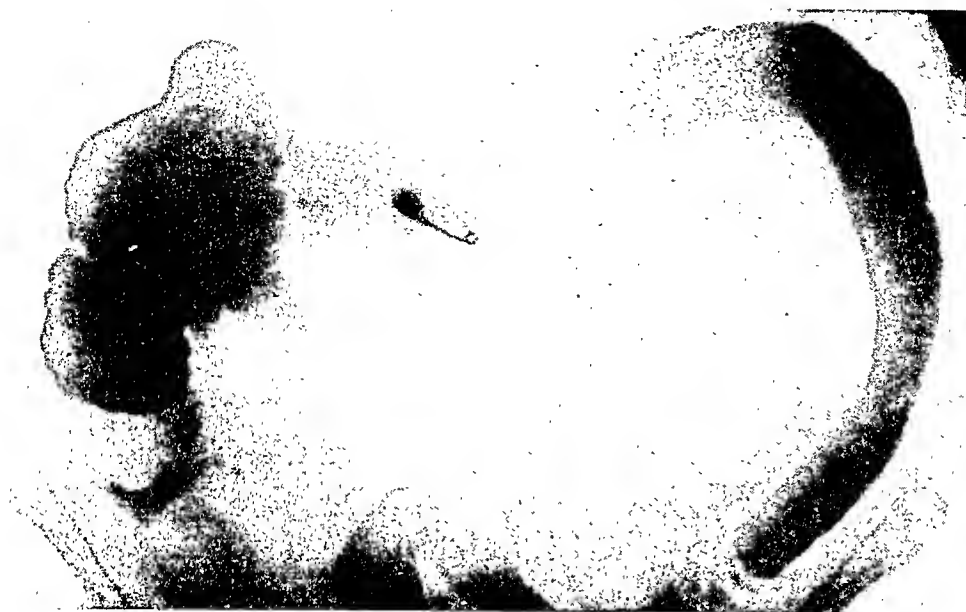


Figure 3. Intestinal obstruction from tumor of the cecum. The gas-dilated loops of small bowel show the "herring-bone" design and are arranged to use a barium enema to differentiate the large from the small bowel.

Localized paralytic ileus affecting only the loops of bowel surrounding a walled-off area of infection, simulate roentgenographically the gas-filled bowel seen in obstruction. As a rule, however, the loops of bowel are not as distended. Localized pain and extreme tenderness on palpation over the involved area is invariably present. There is no general distention but usually some interference with bowel action. Fever and other signs of infection are present.

Localized spastic ileus may produce a similar appearance showing varying amounts of gas-distended small bowel, without involvement of the colon. This, you will recall, is the criteria for diagnosis of small bowel obstruction and at times, differentiation may be very difficult. In spastic ileus of this type, however, the intestinal loops do not show the extreme dilatation seen with mechanical obstruction.

Localized spastic ileus occurs as a reflex response to abdominal pain such as passage of a calculus, ureteral catheterization, or injury to the peritoneum; the presence or absence of pain then becomes an important differential symptom. Pain from rupture of a tubal pregnancy results in this type of intestinal reaction; at the outstart there is no fever. Later, however, if hemorrhage or infection ensues, peritonitis de-

velops with generalized intestinal dilatation and peritoneal exudation with fever.

ONE of the most difficult conditions to diagnose associated with gaseous distention of the bowel is mesenteric thrombosis. This produces gaseous distention of the small bowel and even varying amounts of the colon (up to the mid-transverse colon if the superior mesenteric artery alone is involved; entire intestinal tract if both mesenteric arteries are thrombosed). Barium enema may show dilatation of the colon up to the mid-transverse portion without obstruction or other cause.

There are two points most helpful in making the diagnosis; first, mesenteric thrombosis is almost always associated with sudden severe pain even from the very outstart. The pain is so persistent and severe that it produces an extreme degree of shock; second, it is frequently associated with chronic valvular heart disease or other condition of the circulation. Gaseous distention and pain are most pronounced with the arterial mesenteric thrombosis, while with venous thrombosis, especially at the onset, no demonstrable gas-filled loops may be present.

We have endeavored to show how a careful



Figure 4. A. Paralytic ileus showing gas-distended loops of bowel affecting all of the intestines, both small and large. The rectum is filled with gas. B. Lateral decubitus position showing fluid levels and exudate between coils. C. Transabdominal position best for showing abdominal exudate.

analysis of the roentgen findings, correlated with certain clinical signs and symptoms will serve to establish the diagnosis in cases where gaseous dilatation of the bowel is a prominent symptom. We have emphasized the use of a barium enema in determining the presence or absence of large bowel involvement in the analysis of the roentgen findings.

OTHER acute abdominal conditions which may or may not be associated with gaseous distention of the bowel will be briefly considered: (1) congenital atresia of bowel, (2) intussusception, (3) carcinoma of the colon suddenly obstructed by fecal matter, (4) rupture of diverticulum of colon, and (5) subphrenic abscess.

Congenital atresia of the bowel usually does not give acute symptoms unless it is complete. If this is the case, the picture produced is similar to small bowel obstruction from any other cause—there should be gaseous dilatation above the point of atresia and the bowel should be empty below—there should not be any gas in the rectum.

Intussusception produces acute abdominal pain, nausea, severe prostration, and at times bloody mucus stools. Abdominal palpation or

rectal examination may disclose this to be the advancing head of an intussusception. Unless the intussusception causes intestinal obstruction, gaseous dilatation will be absent. Barium enema, however, will readily disclose the crescentic rounded outline of the barium as it spreads out over the advancing head of the intussusception. Ringlike shadows within the dilated bowel are characteristic of this condition.

Carcinoma of the colon, as insidious as it usually is, may assume very acute manifestations if the small remaining lumen is suddenly occluded by fecal material. Barium enema examination discloses the carcinomatous character of the lesion and may even dislodge the fecal material and open the obstruction.

Rupture of a diverticulum of the colon usually occurs in the sigmoid region, the most frequent site of diverticulitis of the colon, resulting in severe acute abdominal symptoms. Such ruptures are usually not attendant with gas free in the abdomen. The prevalence of diverticulitis of the sigmoid in older individuals (referred to clinically as left-sided appendicitis) is well known so that the examiner may be on his guard in giving cathartics or enemas. If the diagnosis is doubtful or if barium enema is given, usually only a very tiny amount is seen extending beyond



Figure 5. Wherever there is intense pain the findings must be analyzed carefully. Ruptured tubal pregnancy with pelvis filled with blood prevented filling of rectum by gas and gave pattern of possible intestinal obstruction when it was really due to paralytic ileus. Mesenteric thrombosis may also give confusing picture.

the confines of a diverticular sac. In most cases an inflammatory mass has already formed, well walled off by the surrounding tissues.

Subphrenic abscess—If a subphrenic abscess is attended with gas from a gas-producing organism, then x-ray examination in the upright and lateral decubitus positions will readily disclose the gas with a fluid level. In most instances, however, there is no associated gas; there is merely immobilization of the diaphragm in a high posi-

tion. Such splinting of the diaphragm is merely a defense reaction against pain since either the visceral pleura or peritoneum must be involved to cause such reaction. The immobilization of the diaphragm in a high position in itself does not imply subphrenic abscess for such reaction uniformly follows operative procedure or any other insult to the parietal pleura or peritoneum.

There is only one way in which infection of the subphrenic space can be demonstrated and that is by the aid of artificial pneumoperitoneum. A few pumpsfull of air in the abdominal cavity is all that is required. In the upright or lateral decubitus position the air thus introduced will pass freely into the subphrenic space if it is normal and uninvolved, whereas, if it is the site of inflammation the adherence of the diaphragm to the upper surface of the liver or spleen will prevent access of the air to this region.

DEEP-SEATED infection frequently produces sympathetic effusions in adjacent synovial cavities, and subphrenic abscess may thereby give rise to basal exudates in the pleural cavity. Fluid aspirated in such cases is frequently clear but it usually contains polymorphonuclear leukocytes. In such cases artificial pneumoperitoneum is necessary to determine if the pleural effusion is associated with a pyogenic infection below the diaphragm or if it is a simple pleural exudate. A great deal depends upon the outcome of the examination.

This method of examination has been urged for many years but has not come into general use. Surgeons seem reluctant to use artificial pneumoperitoneum in the presence of possible infection in the subphrenic region but we have never, in over twenty years experience, seen it cause any difficulty or spread of the infection. The small amount of air used exerts such a minimal amount of pressure that the most delicate adhesions remain unaffected. The information afforded by this method far outweighs any theoretical disadvantage.

The Xiphosternal Crunch

ITS RECOGNITION AND UNFORTUNATE ROLE IN LIFE INSURANCE AND EMPLOYMENT REJECTIONS

MYER SOLIS-COHEN*

UNIVERSITY OF PENNSYLVANIA GRADUATE SCHOOL OF MEDICINE, PHILADELPHIA

IT is a great tragedy that persons in perfect health are rejected when applying for employment, for life insurance, or for service with the armed forces merely because of a heart sound that has no pathologic significance.

In a considerable proportion of individuals, both well and sick, a crunching sound can be heard over the lower portion of the sternum and over the xiphoid cartilage, slightly to their left. In almost half the cases in which it is present, this xiphosternal crunch is so faint that it may not even be noticed. In the remainder, however, it is fairly loud, and in about one-fifth of the cases its presence is very marked. Many physicians, mistaking it for the murmur of valvular or congenital heart disease or for pericardial friction, subject their patients to prolonged unnecessary treatment and restriction of activity. On observing it, insurance examiners have rejected normal applicants or raised their rating, company doctors have denied employment to persons in good health, and medical officers have refused to admit to the armed services men and women who have no actual physical defect.

*Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine, Philadelphia, and Assistant Director of Public Health, Philadelphia.

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My attention was first directed to this sound forty-five years ago, when I was an assistant in the medical dispensary of the University of Pennsylvania Hospital. I heard a peculiar heart sound that I could not identify and which my superiors could not explain. When invited to present a paper before the Lehigh Valley Medical Society in 1903, I spoke on "A Xiphosternal Crunching Sound with a Report of Six Cases," and published the paper in the American Journal of the Medical Sciences. In reviewing the medical literature of the previous eighty years, I found no description of the sound in any book on general medicine. However, I did find reference to it in one book on physical diagnosis and in several books and articles on the heart.

I have never been able to connect the crunch with any clinical symptom or pathologic condition, although in 1909 I made and published an analysis of sixty-three cases. Since then I have observed the phenomenon in hundreds of my patients, some of whom were rejected for military service in World War I because of it. It was not until four or five years ago, however, when I served on the heart and lung section of the medical examining board of an Armed Forces Induction Center, that I had an opportunity to examine the hearts of large numbers of supposedly healthy individuals. The xiph-

sternal crunch was audible in 17.8 per cent and I found that, for this reason, men with normal hearts were being rejected by able and competent internists and cardiologists. On questioning those presenting this sound, I learned that some of them had been rejected for employment or life insurance and that others had been treated for a cardiac lesion at a great expense of time and money.

I BEGAN to keep notes on all those showing the crunch, and when I had examined 5,000 men, I studied these notes and published the results in the American Journal of the Medical Sciences. Before writing that article about two years ago, I examined most of the books and articles on physical diagnosis, cardiology, and heart sounds published during the previous 125 years. I discovered thirty-one references to what seemed to be the xiphosternal crunch and ten references to what may have been that sound.

It seemed to me that many writers who discussed the murmur of relative or functional tricuspid insufficiency had mistaken the xiphosternal crunch for such a murmur, especially those who regarded incompetency of the tricuspid valve as a common occurrence. I also feel that the cardiorespiratory murmur about which so many authors write is, in many instances, the xiphosternal crunch. Many cardiologists mention only the cardiorespiratory murmur when referring to accidental murmurs. The leaflet on "Examination of the Heart," published by the American Heart Association, describes temporary systolic murmurs produced by infections or other causes of ill health, which sometimes are apical, at other times heard over the whole precordium, and sometimes localized to the left of the sternum or to its lower portion.

Why such a common phenomenon is seldom noticed and why it is ignored by most writers on cardiology, medicine, and physical diagnosis is difficult to explain. One can understand how it would be missed by cardiologists who listen only at the apex and at the base of the heart and fail to include the xiphoid car-



MYER SOLIS-COHEN

tilage. It is quite possible that expert cardiologists, knowing the crunch has no pathologic significance, do not hear it at all, having trained themselves to recognize only pathologic sounds and to ignore all others.

How can one expect a physician to be on his guard against a heart sound about which he was taught nothing in medical school and which is not mentioned in his books or journals? It is not surprising that when many hear the xiphosternal crunch they regard it as evidence of cardiac pathology.

The xiphosternal crunch, when fairly loud, is not difficult to recognize. It has a characteristic crunching, creaking, rubbing, grating, scratching, brushing, or clicking sound. Schwab, Smiley, and Meyn describe it also as a spitting sound. Other adjectives that have been used to describe it are rasping, buzzing, flapping, clacking, whizzing, tapping, vibrating, high-pitched, rough, short and quick, superficial, dry, stiff, harsh, short and rough, musical, and extracardial. It has been called a chisel-sound, a metallic click or tinkling, a

creak, a gastric tinkle, an after-tone or echo, a reduplication, a coin sound, the word "ching," and a murmur. I have compared it to the sound made by a foot crunching in soft snow. Others have compared it to the sound made by striking the clasped hands against the knee, by a chisel or short plane used forcibly across the end of a piece of timber, by a file drawn over wood, by the rubbing together of two pieces of velvet, by drawing a cork out of a bottle, by allowing a stiffly starched cuff to rub slightly against the other while they are on the wrist, by the knock of a motor, by the creak of leather of a new saddle under the rider, and by placing the palm of the hand over the ear and percussing the occiput with the end of the index finger.

THE variations represent how the crunch sounded to different observers as well as in different subjects. Despite its variants, the sound can be recognized easily when distinct, although when faint it may be unnoticed by an ear not trained to detect it. However, when faint, it is seldom mistaken for a pathologic sign. It has a superficial quality, as if produced close to the ear or occurring outside the heart.

The crunch has accompanied systole in most of the cases I have examined, although others have heard it also in diastole, and frequently becomes more pronounced when the subject leans forward. Its intensity occasionally increases with exercise, nervousness, excitement, or fear. In many instances the sound diminishes or even disappears when the patient lies down. Pressure of the stethoscope has not been shown to influence the sound.

The xiphosternal crunch should not be confused with a cardiorespiratory murmur, as it occurs not only during breathing, but also when the breath is held. Its intensity sometimes varies with the different phases of respiration and it is frequently heard best at the end of expiration. If the patient breathes slowly and deeply, a cardiorespiratory murmur will often disappear completely at some point in the respiratory circle, while the xiphosternal crunch will not.

The location of the crunch is typical. The maximum intensity of the sound will almost always be found over the lower end of the sternum and over the xiphoid cartilage and an inch or so to their left. A loud crunch is often transmitted to the left, in a few instances as far as the mid-precordium and occasionally even to the apex of the heart. In these cases it is easily mistaken for the murmur of mitral insufficiency. However, one has only to carry the bell of the stethoscope to the right as far as the sternum to note a gradual increase in intensity if the sound is a crunch, and a gradual diminution if the origin is in the mitral valve.

On the contrary, when the stethoscope is moved to the left, the crunch will diminish and disappear, for it is never heard in the axilla. If the sound heard over the sternum has its origin in the aortic or pulmonic valve it will increase as the stethoscope is moved up from the ensiform cartilage to the base of the heart, while the xiphosternal crunch will diminish.

The apical systolic murmur, considered a normal phenomenon in young persons, is of a blowing quality and, unlike the crunch, is not constant from day to day. Organic systolic murmurs at the apex are rough, not crunching, and do not seem superficial. They are sometimes accompanied by a thrill, which does not occur with the xiphosternal crunch. The latter has been mistaken for the murmur of congenital heart disease, but its character and location should serve to differentiate it.

The superficial and rubbing quality of the xiphosternal crunch has resulted in its being diagnosed occasionally as a pericardial friction, but the latter has a to and fro sound occupying both systole and diastole.

Although they have the same location, the xiphosternal crunch should not be confused with the murmur of tricuspid insufficiency, whether organic, relative, or functional, owing to the absence of the symptoms usually associated with the latter, such as pulsation in the vessels of the neck and an enlarged, tender, and pulsating liver. I believe that the common diagnosis of incompetence of the tricuspid valve is in many instances the xiphosternal crunch.

Aids in differentiating the xiphosternal crunch from organic murmurs are the absence of a cardiac history or of cardiac symptoms, the presence of a normal cardiac rhythm, and a heart of normal size. In doubtful cases the x-ray and the electrocardiogram may also prove helpful.

The cause of the xiphosternal crunch is not known. Many explanations have been offered, suggesting its origin in the heart, in the pericardium, or in the outside tissues. Among the less fantastic causes offered are vibrations of the chordae tendineae produced by imperfect contraction of their muscular attachments and permanent lack of tone. Some regard the phenomenon as a valve sound, a cardiomuscular sound, or a drawing out of the scratch of the second aortic sound.

The causes believed to be in the pericardium include a fibrous patch or white pericardial patch or "milk spot," a rubbing of the visceral over the parietal lamina, and localized precordial roughening.

Those who place the cause outside the pericardium suggest friction of the heart against the chest wall, crowding of the heart—enlarged or distended with blood—in the inferior mediastinum, downward displacement of the heart due to emphysema, mediastinal emphysema—the air in the tissues causing a crepitant sound, movement of the xiphoid, changes in the tension of the loose cellular tissue in the sternoprecordial ligament which binds the anterior surface of the pericardium to the posterior thoracic wall, and gastric resonance imparted to the right ventricle of the heart through the diaphragm. Schwab, Smiley, and Meyn proffer the explanation that the sound is produced by movement of the seventh costal cartilage at the point of articulation with the sternum and the xiphoid process. All observers are in agreement that the xiphosternal crunch has no pathologic significance.

Ninety-one years ago, Brown recorded that "a chisel sound at the lower end of the sternum is of frequent occurrence in persons who are in good health in all respects excepting dyspepsia."

In his book on "The Diagnosis of Diseases of the Heart and Thoracic Aorta," published in 1892, Sansom wrote: "There can be no doubt that short, rough, systolic, seemingly very superficial sounds are often to be heard over the situation of the right ventricle in conditions which deviate in no notable way from the standard of health."

William Osler, discussing Hare's paper on "An Undescribed Cardiac Sound" at a meeting of the Association of American Physicians in 1901, said: "There is a distinct difference in the majority of healthy hearts between the first sound over the apex and that as you move toward the sternum, a more crunching sound, which is peculiar and remarkable."

Colbeck in his book on "Diseases of the Heart," published that same year, stated that a peculiar form of friction sound is sometimes heard over the right ventricle at the level of the fifth and sixth intercostal spaces, close to the left sternal edge and over the base of the ensiform cartilage, often present under apparently normal conditions.

Thirteen years later Blumer wrote: "This peculiar quality of the heart sounds underneath the sternum and in its neighborhood seems to be worthy of emphasis because the phenomenon is a normal rather than a pathological one, and because under certain conditions it may be mistaken for a pathological sound and give rise to errors in diagnosis. I have noted the almost constant presence of the sound in all sorts of cases for a number of years."

KING in 1919 said that the crunch is a common phenomenon of the normal heart and may be observed in most hearts, particularly in the leaning forward position. It was observed commonly by him in normal soldiers and in men with irritable hearts. King repeated this information in "The Practitioner's Library of Medicine and Surgery" in 1932, in "The Cyclopedia of Medicine, Surgery and Specialties" in 1939, and in Stroud's "The Diagnosis and Treatment of Cardiovascular Disease" in 1940.

Norris wrote in 1924: "In a considerable

number of perfectly healthy individuals the heart sounds heard just over the costiform cartilage and in its immediate vicinity have a peculiar harsh, scratching, scraping, or crunching quality resembling a pericardial friction sound."

Schwab, Smiley, and Meyn, in a recent investigation as yet unpublished, found the sound in 3.3 per cent of more than 3,000 Army separeatees.

I am not the only one who has seen the xiphosternal crunch diagnosed as an organic murmur. Similar mistakes were reported by Laennec in 1826, Gairdner in 1862, Sutton in 1867, Broadbent in 1897, Benedict in 1910, Blumer in 1914, King in 1919, 1932, and 1939, and Norris in 1924.

Whether you examine applicants for life insurance, or for employment, or the armed forces, or have a patient in your office, you ask questions about all the diseases he has had. If he has never had growing pains in childhood, rheumatism, pains in the joints or muscles, shortness of breath or palpitation on exertion, swelling of the feet, signs of heart disease, or heart consciousness, you consider him a good risk. You get out your stethoscope and listen over the apex; you listen again and you do not hear anything abnormal; you listen at the aortic and pulmonic areas. Fine! Too many cardiologists stop there.

THE CARDIOLOGIST in charge of the cardiac ward of one of our naval hospitals stated that he never listened at the xiphoid cartilage when he examined a patient. When an examiner listens at the xiphoid cartilage he hears a peculiar sound. Sometimes he finds this sound at the apex, and because that is the only place he listens, he calls it a systolic apical murmur. If he would carry his stethoscope over further, he would find the sound getting louder and louder with a very definite crunch, and if he went on over to the left it would disappear. In systole, of course, he would hear it. He would get the borders of the heart and find that they were normal; he would feel the pulse and that would be normal. He would have the man lie

down, expecting the murmur to be louder in some cases, but on the contrary, it would become softer, and perhaps disappear. He would have the patient lean forward and in some cases he would find it getting louder. He would find by these few little manipulations that it is not a cardiac murmur.

It is difficult to understand why books on physical diagnosis, the modern books on cardiology, with the exception of Stroud's, and articles on heart sounds, especially peculiar heart sounds, make no mention of the xiphosternal crunch. Two prominent cardiologists, in two articles on peculiar heart sounds, mentioned about twenty but never this one.

It is a peculiar heart sound, difficult to understand, and seemingly harmless. Some of my patients were rejected in World War I, but I did not fully realize the importance of the situation until I served in the heart and lung section at a large induction center in Philadelphia, and again in a smaller one in Camden, and found capable doctors rejecting men because of the xiphosternal crunch. Although none of these doctors had heard of it, they were all interested, and those who came on the days I was there became very well acquainted with it and could detect it as well as I could.

When men who had been rejected on a day when I was not there were reexamined, I found that all they had was a xiphosternal crunch; it was then that it seemed to me very important that it be brought to the attention of the profession. For this reason I took notes on all the patients, because before that time I did not realize that the sound occurred in normal people. Most of the people who come to my office are sick and I had been trying to find the pathologic condition associated with the sound. It was somewhat of a revelation to find that so many of these so-called normal hearts (I say "so-called" because we all know that those examined at the induction boards were not all really normal) showed this sign. It seemed very important, and that is why I deemed it necessary to bring it to the attention of the medical profession.

Cholecystography in Diagnosing Small Calculi and Stones

ADOLFO J. BURLANDO*

CENTRAL MILITARY HOSPITAL, BUENOS AIRES, ARGENTINA

CHOLECYSTOGRAMS made in the usual prone position often fail to reveal small stones or tumors when the gallbladder fills completely with the dye.

The density of the vesicular shadow may totally obscure small cholesterol calculi or small intravesicular tumors.

For more than ten years we have used the same procedures for the roentgenologic study of the gallbladder as for the duodenal bulb: fluoroscopic examination and instantaneous serial roentgenograms.

Fluoroscopic examination permits us to localize the vesicular shadow with relation to neighboring

structures, to manipulate or compress the gallbladder region and obtain the clearest view.

In the standing position, concentrated bile and iodine is heavier than cholesterol concretions, which consequently are suspended, and produce a clear, translucent band that is very easily interpreted.

We have selected from our files some cholecystograms which demonstrate the great diagnostic difficulties with the usual roentgenograms, and the clarity with which the small suspended cholesterol calculi and the papillomas are revealed in the instantaneous roentgenograms that were made in the upright position with compression.

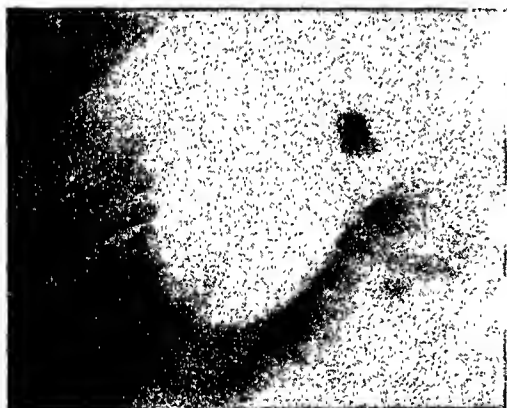


Figure 1 (upper left). Radiographs in prone decubitus. No calculous images are perceived.

Figure 2, A and B (lower left). Same patient: radiographs in upright position, delayed. Suspended cholesterol calculi.

Figure 3 (upper right). Cholecystograph in prone decubitus. Spotted vesicle.



*Chief of Department of Electroradiology, Central Military Hospital, Buenos Aires, Argentina.

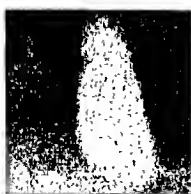
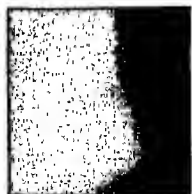
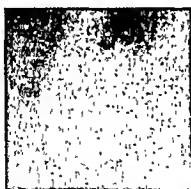


Figures 4 and 5, A and B (top). Cholecystographs of the same patient as in Figure 3 in standing position with distinct inclinations. The plane of the calculi is maintained horizontal.

Figure 6 (left). Cholecystograph in prone decubitus. Same radio-translucent image.



Figures 7, 8, and 9 (left and below). Study of the same vesicle in standing position and in different position grades of rotation. The papilloma is clear and always in the same position relative to the vesicular walls.



RADIOGRAPHIC FACTORS

Radiographs in prone decubitus: diaphragm P. B. Kv. 65-70 plus 70 distance 1 meter. Picture Eastman Blue Brand. Double (filter, screen) reinforced.

RADIOGRAPH DELAYED

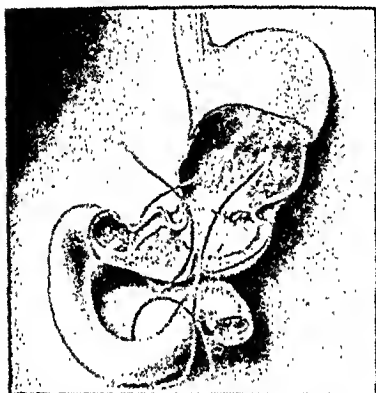
Upright position. Mean distance 70 centimeters. Kv. 65-70 plus 40 (300 milamp.). Double filter (movable, continuous). Eastman picture. Revolving tube of anode.

Transthoracic Vagotomy for Peptic Ulcer

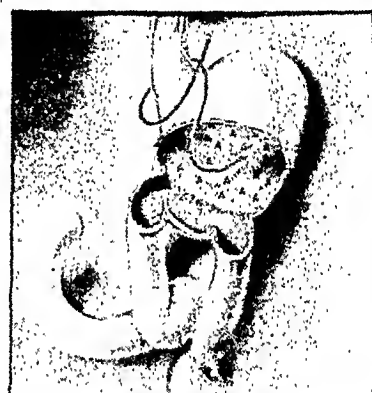
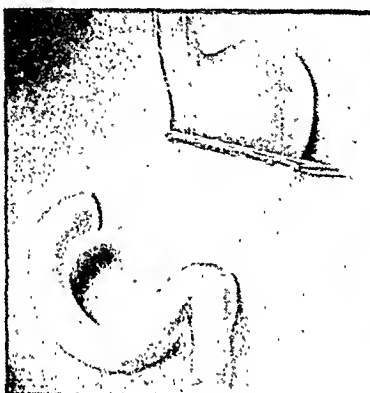
*A scientific exhibit from Grimson, K. S., Baylin, G. J., Taylor, H. M., Hesser, F. H.,
and Rundles, R. W., of the Duke University School of Medicine, Durham, N. C.*

THERE ARE TWO IMPORTANT MECHANISMS THAT MAY INFLUENCE THE DEVELOPMENT AND COURSE OF DUODENAL OR GASTRIC ULCER BY ALTERING MOTILITY AND SECRETIONS OF THE STOMACH:

THE FIRST OF THESE MECHANISMS
IS HORMONAL.



SUBTOTAL GASTRIC RESECTION AFFECTS THIS MECHANISM BY REMOVING THE ANTRUM
AND EXCLUDING THE DUODENUM.

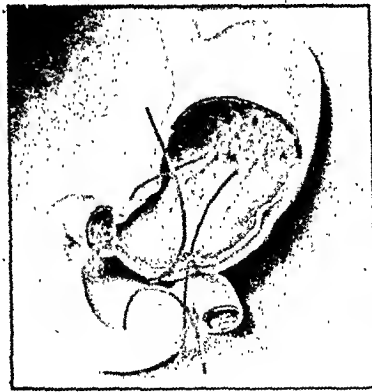
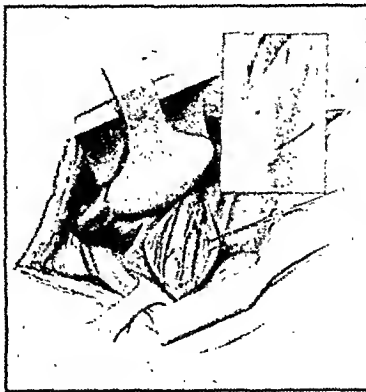


TRANSTHORACIC VAGOTOMY WAS FIRST CONSISTENTLY AND EFFECTIVELY EMPLOYED FOR PEPTIC ULCER IN 1943 BY L.R. DRAGSTEDT. IT HAS BEEN USED IN DUKE HOSPITAL SINCE JUNE 1944.

THE SECOND OF THESE MECHANISMS
IS NERVOUS.

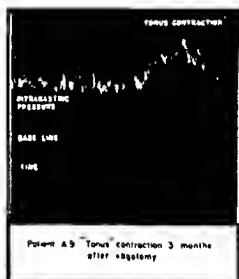
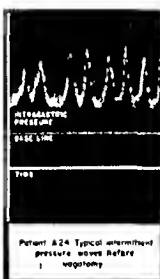
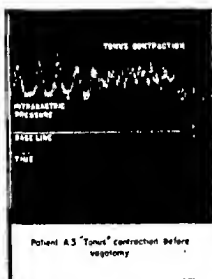
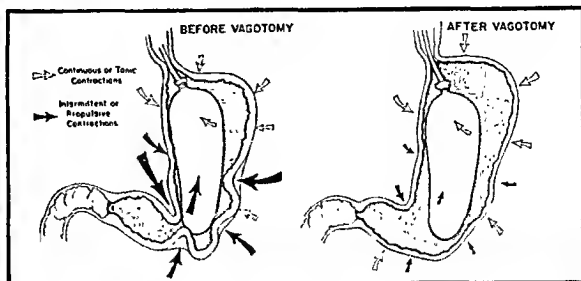
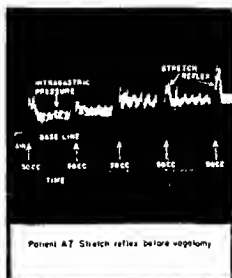


TRANSTHORACIC VAGOTOMY THEORETICALLY BLOCKS NEUROGENIC, PSYCHOGENIC
OR REFLEX STIMULI.



**TRANSTHORACIC VAGOTOMY HAS BEEN PERFORMED UPON 57 PATIENTS.
FOLLOWED 9 TO 36 MONTHS.**

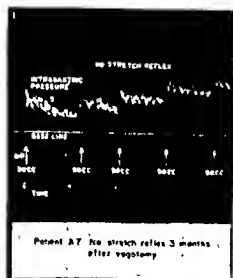
VAGOTOMY ALTERS ACTIVITY OF THE STOMACH AS JUDGED BY BALLOON



CHANGES OF INTRAGASTRIC PRESSURE BEFORE AND AFTER VAGOTOMY
10 human cases with 300 mm of air and pressures recorded by a Brouha-Woodward
(Shaded and converted to cm. of water)

	Before Vagotomy	1-3 mos. After Vagotomy	3 mos. 6 mos. After Vagotomy	6 mos. 1 yr. After Vagotomy
Group A. 4 Patients Tested	10	27	14	6
Average Raising Pressure "Tone Base Line"	4.0 cm.	7.5 cm.	3.1 cm.	2.7 cm.
Average Extension Above Raising Pressure	11.6 cm.	13.0 cm.	7.6 cm.	7.2 cm.
Group B. 4 Patients Tested	1	1	1	1
Average Raising Pressure "Tone Base Line"	4.1 cm.	9.0 cm.	9.1 cm.	7.0 cm.
Average Extension Above Raising Pressure	2.7 cm.	1.2 cm.	1.7 cm.	7.2 cm.
Group C. 4 Patients Tested	2	2	3	1
Average Raising Pressure "Tone Base Line"	7.5 cm.	9.0 cm.	9.7 cm.	9.9 cm.
Average Extension Above Raising Pressure	9.7 cm.	1.6 cm.	9.8 cm.	9.9 cm.
Group D. 4 Patients Tested	1	3	3	0
Average Raising Pressure "Tone Base Line"	7.0 cm.	7.0 cm.	9.9 cm.	1.7 cm.
Average Extension Above Raising Pressure	0.1 cm.	0.5 cm.	1.7 cm.	1.7 cm.
Group E. 4 Patients Tested	6	7	4	1
Average Raising Pressure "Tone Base Line"	4.1 cm.	8.1 cm.	8.7 cm.	6.3 cm.
Average Extension Above Raising Pressure	12.6 cm.	13.0 cm.	10.0 cm.	10.0 cm.

Pain with contractions and stretch reflexes were occasionally observed before but not after operation. Slow "tonus" contractions were observed occasionally before and after vagotomy.





Patient W.S. 10 days after vagotomy immediately after taking barium.



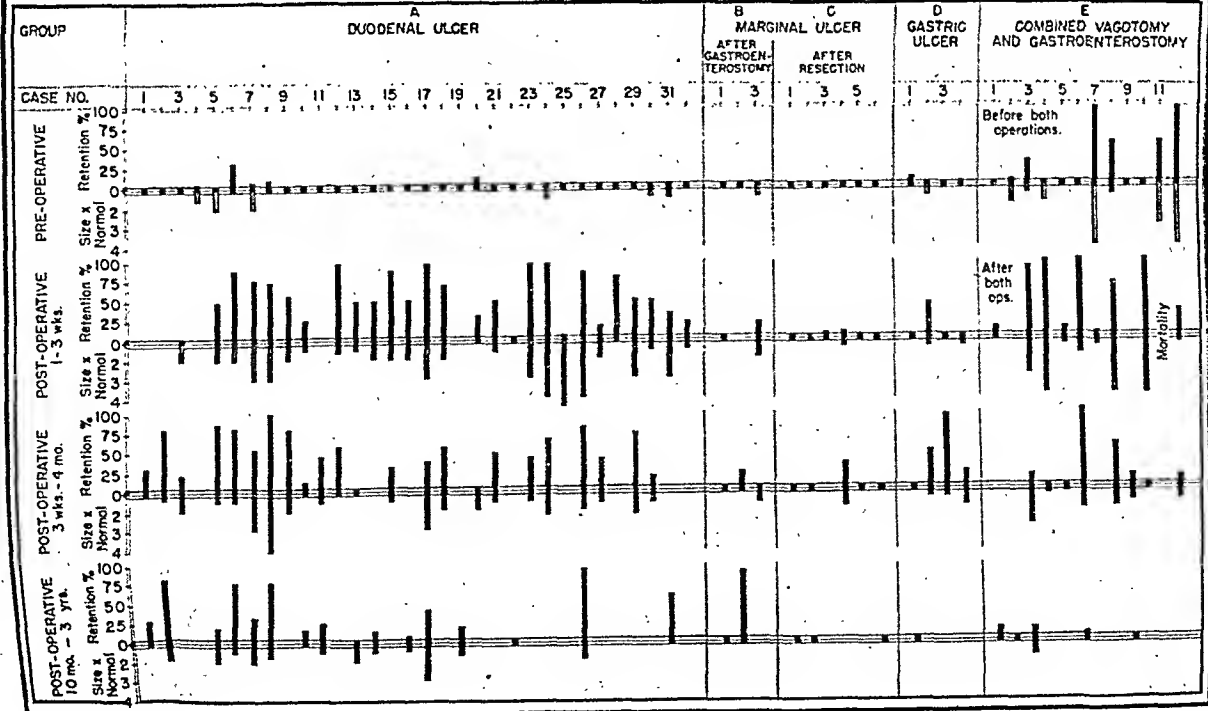
Patient W.S. 10 days after vagotomy 6 hours after taking barium.

VAGOTOMY ALTERS ACTIVITY OF THE STOMACH AS OBSERVED BY X-RAY

EXAMINATION OF STOMACH BY X-RAY AFTER BARIUM MEAL

Number of Patients	BEFORE VAGOTOMY						AFTER VAGOTOMY (1 Week to 4 Mos.)					
	Duodenum		Peristaltic Waves				Peristaltic Waves				Duodenum	
	Visualized	Crater	Hyper-active	Active	Weak	Absent	Active	Slow	Weak	Absent	Visualized	Crater
32 With Duodenal Ulcers	32	16	8	24			6	7	16	1	19	1
3 With Enterostomy Stoma Ulcers	3			3					2	1	1	
6 With Resection Stoma Ulcers					1	4			4	4		
4 With Gastric Ulcer	4			3	1		2	1	1		4	
12 With Combined Operations	9	8	5	3	2	1	1		6	3	2	

CHANGES IN AMOUNT OF 6 HOUR RETENTION OF BARIUM AND IN SIZE OF STOMACH AFTER VAGOTOMY



VAGOTOMY ABOLISHES ULCER PAIN EVEN IMMEDIATELY AFTER VAGOTOMY AND BEFORE ULCERS HAVE HEALED.

PAIN PATHWAYS ARE NOT INTERRUPTED BY VAGOTOMY:

1. Spinal anesthesia high enough to block the splanchnic pathways relieves ulcer pain even though the vagus nerves are intact.

2. Stimulation of the vagus nerves in the lower chest in 2 patients and below the diaphragm in 2 others during operation under spinal anesthesia did not produce abdominal pain.

VAGOTOMY PROBABLY RELIEVES ULCER PAIN BY REDUCING GASTRIC MOTILITY. THIS RELIEF MIGHT BE EFFECTED BY DIMINISHING IRRITATION OF THE ULCER - PRODUCED BY FORCEFUL THRUST OF GASTRIC CONTENT AND BY REDUCTION OF PAINFUL SPASM OF GASTRIC SMOOTH MUSCLE. THIS HYPOTHESIS IS BASED UPON THE FOLLOWING OBSERVATIONS:

NONSPECIFIC EFFECTS OF ANESTHESIA OR OPERATION DO NOT ACCOUNT FOR RELIEF OF PAIN:

1. One patient, after an hour of ethylene ether anesthesia without operation, promptly experienced pain when acid was introduced into the stomach.

2. Several of the patients gave a history of previous appendectomy or cholecystectomy with only temporary relief of pain.

ALTHOUGH ACIDITY OF THE SECRETIONS OF THE STOMACH IS USUALLY REDUCED BY VAGOTOMY, THIS IS NOT THE ONLY EXPLANATION OF RELIEF OF PAIN:

1. 4 patients (B1, C6, D1, & E10) had no free acid before vagotomy but had severe pain.

2. 7 patients (A8, A18, A30, B3, C4, D3, & E9) had little free acid before vagotomy but had severe pain.

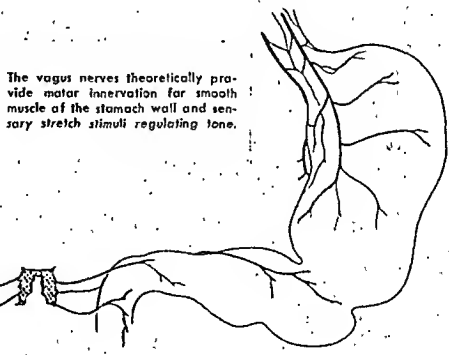
3. Introduction into the stomach of 300 cc. of 0.5% HCl produced pain in 11 patients before vagotomy but did not produce pain after operation. 2 of these patients had gastric ulcers and 3 patients had marginal ulcers.

REDUCTION OF MOTILITY AS JUDGED BY BALLOON TESTS OCCURRED IMMEDIATELY AFTER OPERATION IN EACH PATIENT AND HAS PERSISTED WITH THE RELIEF OF PAIN

1. This explanation is based upon consistency of the effect and exclusion of the three possibilities on the left. Nevertheless, restoration of motility by urecholine has failed to reproduce pain and other explanations may exist.



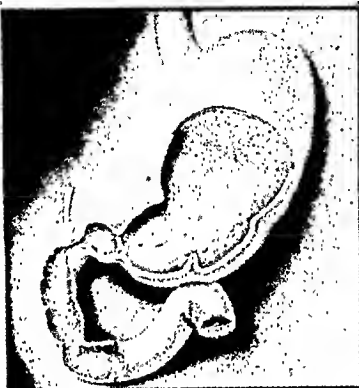
The splanchnic nerves convey sympathetic fibers to the stomach and spinal segmental sensory fibers mediating pain from the stomach.



The vagus nerves theoretically provide motor innervation for smooth muscle of the stomach wall and sensory stretch stimuli regulating tone.

ALTHOUGH EACH OF THE PATIENTS HAS BEEN RELIEVED OF SYMPTOMS OF ULCER, AND ABLE TO TAKE AN UNRESTRICTED DIET, RETENTION OR OBSTRUCTION HAS LED TO A VARYING DEGREE OF CLINICAL DIFFICULTY. RETENTION IS PROBABLY CAUSED BY OBSTRUCTION:

OBSTRUCTION MAY BE CAUSED BY CONTRACTION OF SCAR TISSUE AS HEALING OCCURS.



IT MAY ALSO BE AFFECTED BY ABNORMAL CONSTRICTION OF THE PHYSIOLOGICAL PYLORIC SPHINCTER.



OR THE SPHINCTER MAY RELAX POORLY BECAUSE OF FAILURE OF PERISTALTIC PROPULSIVE STIMULATION.



OBSTRUCTION PRODUCED 50% OR MORE 6 HOUR RETENTION OF BARIUM IN 22 OF THE 36 PATIENTS WITH DUODENAL OR GASTRIC ULCERS TREATED BY VAGOTOMY ALONE THIS IS STILL PRESENT IN THOSE OBSERVED ONE TO THREE YEARS.

OBSTRUCTION PRODUCED 95 TO 100% RETENTION IN ANOTHER 6 PATIENTS WITH DUODENAL OR GASTRIC ULCER AND NECESSITATED SECONDARY GASTROENTEROSTOMY

CONCLUSIONS

1. Healing or quiescence of duodenal or gastric ulcer has usually followed transthoracic vagotomy and most patients are satisfied with the results. Nevertheless, disturbances of gastrointestinal function including gastric retention have occurred frequently and occasionally produced serious complications. Probably, therefore, vagotomy alone should not be used as a standard treatment for duodenal ulcer.
2. Healing or quiescence of stomach ulcer has followed transthoracic vagotomy and since complications caused by retention are less serious, vagotomy may be indicated as standard treatment.
3. Transthoracic vagotomy combined with gastroenterostomy has been followed by healing of ulcer and by a low incidence of symptoms of retention. This requires two operations, however, and probably can be accomplished better by subdiaphragmatic vagotomy through a transabdominal approach.
4. Alterations of motor and secretory functions of the stomach have usually persisted as judged by examination made as long as 3 years after vagotomy.



TRANSABDOMINAL VAGOTOMY IS NOW BEING STUDIED AS A TREATMENT FOR DUODENAL ULCER TO DETERMINE WHETHER ITS EFFECTS ARE AS CONSISTENT OR PERMANENT AS THOSE OF TRANSTHORACIC VAGOTOMY. A DRAINAGE OPERATION IS ADDED TO AVOID GASTRIC RETENTION.

Transthoracic vagotomy can not be properly evaluated as a treatment of ulcer until patients have been observed over a period of many years and until its effects upon the intestine and other abdominal organs are better known.

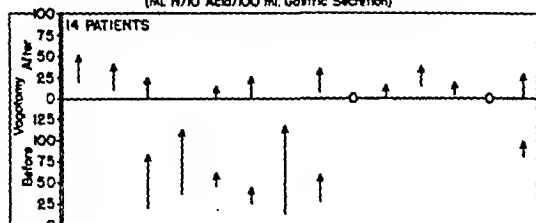
CLINICAL COURSE OF 57 PATIENTS TREATED BY VAGOTOMY

BEFORE VAGOTOMY										AFTER VAGOTOMY									
PATIENT NO.	AGE	DURATION OF SYMPTOMS YEARS	ULCER PAIN	CONSTIPATION	DISABILITY SINCE ULCER	HEMORRHAGE	VOMITING	INTERNAL MONTHS	ULCER PAIN	HEMORRHAGE	VOMITING	BOWEL CONSTIPATION	DIARRHEA	DISABILITY FROM OTHER CAUSES	GAIN IN WEIGHT				
<p>KEY TO TYPES OF DISABILITY AFTER VAGOTOMY:</p> <p>0 - NO CHANGE IN DISABILITY AFTER VAGOTOMY</p> <p>W - WEAKNESS</p> <p>N - NERVOUSNESS</p> <p>P - PAIN CHEST WALL</p> <p>C - COLICUS ABDOMINAL PAIN</p> <p>D - DIARRHEA</p> <p>F - FAULNESS OR DISTENTION OF ABDOMEN</p> <p>E - FULL ERUCTION</p> <p>V - VOMITING</p>																			
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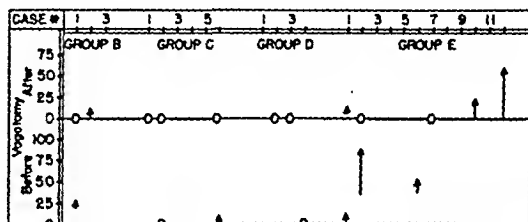
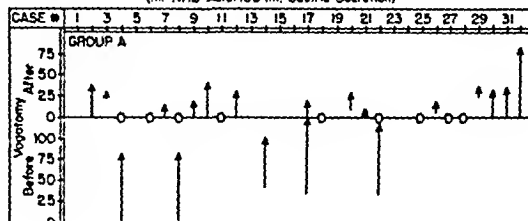
VAGOTOMY ALTERS SECRETIONS OF THE STOMACH OBTAINED BY SUCTION

VOLUME OF GASTRIC SECRETIONS ASPIRATED BETWEEN 8:00 P.M. & 8:00 A.M.								
Vagotomy	GROUP A		GROUP B		GROUP C		GROUP D	
	Before	After	Before	After	Before	After	Before	After
No. Patients Tested	28	26	2	3	5	6	3	3
Maximum Vol. cc.	2540	1700	1650	600	840	500	650	850
Minimum Vol. cc.	105	20	540	25	185	20	10	5
AVERAGE cc.	919	337	1020	352	528	196	553	409

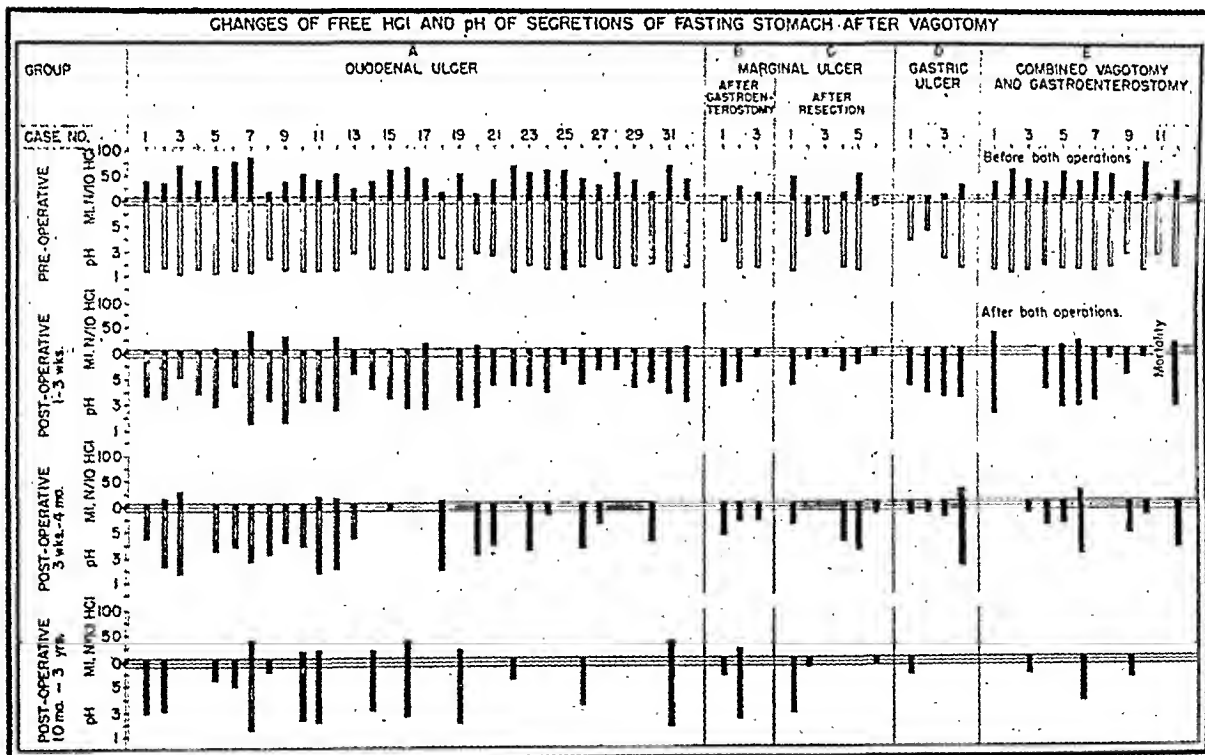
CAFFEINE TEST—Maximum Response—Free Acid
(ML N/10 Acid/100 ml. Gastric Secretion)



INSULIN TEST—Maximum Response—Free Acid—1 week to 4 months
(ML N/10 Acid/100 ml. Gastric Secretion)



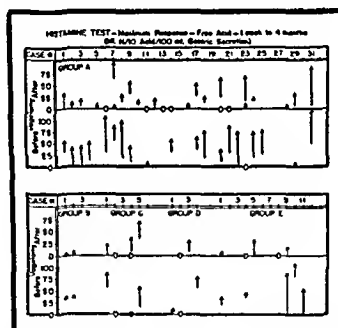
CHANGES OF FREE HCl AND pH OF SECRETIONS OF FASTING STOMACH AFTER VAGOTOMY



VAGOTOMY HAS BEEN COMBINED WITH GASTROENTEROSTOMY IN 12 OF THE 57 PATIENTS

BEFORE COMBINED VAGOTOMY & GASTROENTEROSTOMY

PATIENT NO.	AGE	LOCATION OF ULCER	DURATION OF SYMPTOMS YEARS	ULCER PAIN	HEMORRAGE	VOMITING	CONSTIPATION	DISABILITY FROM ULCER
GASTROENTEROSTOMY WAS CONSIDERED NECESSARY AFTER VAGOTOMY IN 5 PATIENTS								
1	41	Stomo	8	+++	0	+	+	+++
2	41	Duodenum	3	++	++++	+	+	+++
3	29	Duodenum	10	+++	0	+++	0	+++
4	58	Duodenum	12	++++	0	+++	+	+++
5	52	Antrum	5	++++	++	+++	0	+++
GASTROENTEROSTOMY WAS CONSIDERED ADVISABLE AT TIME OF VAGOTOMY IN 5 PATIENTS								
6	46	Duodenum	10	+++	0	+	+	++
7	34	Antrum	8	++++	0	0	+	+++
8	63	Duodenum	10	++++	0	+++	+	++++
9	43	Duodenum	20	+++	+	+++	+	+++
10	55	Duodenum	30	++++	++	+++	+	++++
GASTROENTEROSTOMY WAS PERFORMED BEFORE VAGOTOMY IN 2 PATIENTS								
11	53	Antrum	23	+++	0	0	0	++
12	49	Duodenum	28	+++	++++	+++	0	+++



GROUP E

AFTER COMBINED VAGOTOMY & GASTROENTEROSTOMY

TYPE OF GASTROENTEROSTOMY	INTERVAL BETWEEN OPERATIONS	INTERVAL AFTER OPERATIONS	ULCER PAIN	HEMORRAGE	VOMITING	BOWEL HABIT	DIARRHEA	DISABILITY FROM ULCER	OTHER CAUSES	GAIN OF WEIGHT
RESULTS										
Pyloroplasty	105 days	27 mos.	G 0	0	0	0	0	0	++WNC	-6
Jejunostomy	26 days	26 mos.	G 0	0	0	0	+G	0	0	+35
Pyloroplasty	11 days	20 1/2 mos.	G 0	0	0	+C	+G	0	0	30
Pyloroplasty	14 days	17 mos.	G 0	0	0	0	0	0	0	+26
Pyloroplasty	29 days	8 mos.	G 0	+	0	0	0	0	WNC	0
Jejunostomy	0 days	18 mos.	G 0	0	0	0	++T	0	0	25
Pyloroplasty	0 days	13 1/2 mos.	G 0	0	0	0	++T	0	0	36
Pyloroplasty	0 days	11 mos.	G 0	0	0	0	0	0	0	-2
Exclusion	0 days	10 1/2 mos.	G 0	0	0	0	+G	0	0	+10
Pyloroplasty	0 days	23 days	5	Mortality						
Pyloroplasty	63 days	10 1/2 mos.	G 0	0	0	0	+T	0	+WPE	0
Exclusion	33 days	10 mos.	G 0	0	0	0	0	0	+W	-7

Bacteriologic, Etiologic, and Serologic Studies in Epilepsy and Schizophrenia II.

EFFECTS IN ANIMALS FOLLOWING INOCULATION OF ALPHA STREPTOCOCCI

EDWARD C. ROSENOW

LONGVIEW HOSPITAL, CINCINNATI

THE occurrence of convulsions and of psychotic symptoms in low incidence during various infective diseases, some due to neurotropic viruses as now understood, has been considered as presumptive evidence in favor of an infectious etiology of epilepsy and schizophrenia.¹⁵ The possibility that specific types of streptococci might in some way be causative was suggested in experiments on elective localization and specificity of alpha streptococci as isolated in studies of diseases of the nervous system.

Streptococci isolated from patients with infectious peripheral neuritis, when given intravenously to rabbits localized and produced lesions in the peripheral nerves.^{1, 2} The streptococci isolated in studies of herpes zoster, a disease now considered to be due to a virus, localized and produced lesions in the posterior columns of the spinal cord and intervertebral ganglia associated with blistering of the skin and great pain characteristic of that disease.³

The streptococci isolated in studies of intercostal neuralgia localized in posterior roots of intercostal nerves of rabbits on intravenous injection.⁴ The streptococci freshly isolated from a dying pulp of a tooth and from an excised piece of inflamed muscle

in a patient suffering from a recurrent severe attack of dental neuritis and myositis localized electively in the pulps of teeth, the dental nerves, and muscles of rabbits and dogs following intravenous injection.⁵

Spasms of the diaphragm were produced consistently on intracerebral inoculation of living cultures, the heat-killed streptococci, and filtrates of active cultures of the streptococcus as isolated in studies of epidemic and persistent postoperative hiccup.⁶ Postoperative "ether convulsions" have been reproduced experimentally with a specific type of neurotropic streptococcus.⁷ Alpha streptococci freshly isolated from nasopharynx, stool, spinal fluid, and the virus of poliomyelitis on appropriate injection produced flaccid paralysis in guinea pigs, rabbits, and monkeys as the outstanding manifestation,⁸ whereas the streptococci similarly isolated in studies of encephalitis^{9, 10} produced the symptoms of encephalitis often corresponding in type to the encephalitis in the patient from whom the streptococci was isolated.¹¹

The symptoms and lesions characteristic of Sydenham's chorea were produced in rabbits on intracerebral and intravenous injection of the streptococcus isolated from the nasopharynx of patients suffering from Sydenham's chorea, and were produced in dogs through the induction of chronic foci in the teeth with the streptococcus.¹² Spasmodic

This is second of a series of three papers by Dr. Rosenow in which are recorded the results of bacteriologic and experimental studies on the etiology of epilepsy and schizophrenia. The third paper will appear in a later issue of *Postgraduate Medicine*.

torticollis was produced in high incidence in rabbits,¹³ and the strange syndrome of respiratory arrhythmia and mental deterioration following encephalitis was closely simulated¹⁴ on intracerebral injection of the streptococci isolated from the nasopharynx of respective patients.

It should be emphasized that these highly specific results were obtained by the use of special methods. The usual methods did not suffice.¹⁵ Other workers who have used methods essentially like those we have used have reported similar highly specific results in a wide range of diseases, involving tissues derived from both mesoderm and ectoderm. Numerous reports by different investigators deal especially with the question of specificity of alpha streptococci in the causation of disease.*

The concept has been set forth that highly specific types of streptococci may be causative in epilepsy and schizophrenia; for this concept to be valid, proof is needed to show that such specificities may be acquired and that perhaps hereditary predisposition may provide the very conditions favorable for streptococci to acquire the respective specific properties. Experimental evidence is not lacking to show that changes in specificity of alpha streptococci do occur in response to changes in environment. The continual presence of neurotropic and arthrotropic alpha streptococci, respectively, in patients having "neuropathic" or "arthropathic" hereditary predispositions and suffering from chronic encephalitis and chronic arthritis, respectively, has been shown.³¹

Changes in vitro from one type of specificity of alpha streptococci into other types often characteristic of those at hand in, or the cause of, epidemic diseases have been shown to occur seasonally,³² and have been induced by growth on certain artificial mediums,¹ by successive passage through animals,³³ and by exposing cultures to a high-frequency field of radiant energy.³⁴ Changes in localization of the freshly isolated streptococci in rabbits following intravenous injection matched changes in localization which occurred spontaneously in patients during successive outbreaks of epidemic hiccup and of



EDWARD C. ROSENOW

neuromyeloencephalitis.³⁵ The importance of the principles of microbic dissociation in the causation of disease in accord with these experiments has been especially emphasized by Hadley.³⁶

LOCALIZATION in animals on injection of living cultures of streptococci, the heat-killed organisms, and the toxic components in filtrates of cultures in my studies were often so precise as to resemble the specific pharmacologic action of drugs and chemicals.³⁷

Streptococci isolated from the nasopharynx and infected pulpless teeth of persons suffering from epilepsy and schizophrenia have been shown to possess neurotropic distribution curves of cataphoretic velocity.³⁸ A number of persons who were in the early stages of epilepsy and of psychoneurosis recovered following therapeutic injections of autogenous vaccines prepared from streptococci with neurotropic cataphoretic velocity³⁹ and one which had produced spasms or mental disorientation, respectively, in rabbits on intracerebral injection.

*Haden,¹⁶ Barnes and Giordano,¹⁷ Nickel and Hufford,¹⁸ Cooper,¹⁹ Harby and Brinch,²⁰ Welch,²¹ Meivier and Gardner,²² Cook,²⁴ Bernhardt,²⁵ Irons, Brown, and Nadler,²⁶ Kelly,²⁷ Topley and Weir,²⁸ Wilkie,²⁹ and Jones and Newson.³⁰

It is the purpose of this paper to describe the methods used, to record unpublished experiments on *Macacus rhesus* monkeys which had been inoculated with streptococci from diverse sources, and to report results obtained in a bacteriologic study of epilepsy and schizophrenia and of the localization in animals of the respective streptococci as isolated.

METHODS

Nasopharyngeal swabbings of patients suffering from various diseases, including epilepsy and schizophrenia, were made with aluminum-wire-wrapped swabs bent to a suitable angle so as not to touch the tongue. Pus from tonsils was expressed and scooped with a small bent laryngeal mirror. Purulent material from the depth of pyorrhea pockets was aspirated into capillary pipettes. Severed apices of pulpless teeth were extracted in a sterile manner. Each of these materials was suspended in 2 ml. of a 0.2 per cent gelatin-Locke or isotonic sodium chloride solution for cultures, precipitation tests, and inoculation of animals.

Cultures were made from spinal fluid, from the centrifuged sediment of freshly voided urine, and from suspensions of stool in sodium chloride solution. The surface of horse blood agar plates was inoculated routinely, and serial dilution cultures³⁹ were made in mediums affording a gradient of oxygen tension, usually alternately in dextrose-brain broth (0.2 per cent dextrose) and soft dextrose-brain agar (0.2 per cent dextrose and 0.2 per cent agar) in tall (12 cm.) columns in test tubes ($\frac{1}{8} \times 6$ or 8 inches). The dextrose-brain broth and dextrose-brain agar were usually freshly prepared by adding before autoclaving approximately 1 part by volume of pieces of fresh or frozen calf or young beef brain to approximately 7 volumes, or 15 ml., of the medium, previously adjusted to pH 7.2 and then autoclaved at 15 pounds pressure for twenty minutes.

The amount of inoculum in the first tube and the degree of serial dilution was determined roughly by the number and kind of organisms found in Gram-safranin stained films of the material under study. Serial, one hundredfold, dilutions or 10^{-2} of the materials suspended in sodium chloride solution were usually made by transferring 0.15 ml. from tube to tube with a 1 ml. pipette, and 10,000 fold or 10^{-4} dilutions of cultures were made by transferring 1.5 ml. from tube to tube with nichrome wire. The same pipette or wire was used for the serial dilutions without sterilizing between transfers. Hence, the successive dilutions represent dilutions of liquid and not necessarily corresponding dilutions of organisms.

Seven ml. of blood were routinely drawn from the vein at the bend of the elbow into sterile vacuum tubes. The blood was allowed to clot. The rubber stopper was then removed, in a sterile manner, the clot loosened with a sterile capillary pipette, the rubber stopper replaced, and the vial centrifuged. The serum was decanted then, and in a sterile manner, the partially macerated clot was transferred into 200 ml. of freshly prepared dextrose-brain broth. The small amount of blood remaining in the stoppered vial and the inoculated dextrose-brain broth were then incubated. Gramsafranin stained films were made

and examined for bacteria as soon as evidence of growth in the broth had occurred, and in five or seven days such films were made from the blood residue in the vial and from the sediment of seemingly negative cultures. All cultures were incubated at 33°C. to 35°C.

Pure cultures of the streptococci for inoculation of animals and other studies were obtained not from primary blood agar plates, but from the end point of growth of usually young primary serial dilution cultures alternately in dextrose-brain broth and dextrose-brain (agar or from young primary cultures in dextrose-brain) broth. Blood agar plates were made of these to determine the type of streptococcus and to check the purity of the cultures.

MONKEYS were inoculated intracerebrally usually with 1.5 ml. of the washings of nasopharyngeal swabbings of patients, of corresponding pure cultures in dextrose-brain broth or autoclaved chick embryo medium of the streptococci diluted 1:200 or more, and of emulsions or filtrates of emulsions of the brains and spinal cords of mice, rabbits, or monkeys that had succumbed to poliomyelitis, polio-encephalitis, or encephalitis following intracerebral inoculation. In some instances intraspinal, intravenous, and intramuscular inoculations were given in addition to intracerebral inoculations.

Inoculations were repeated at short or long intervals as indicated by the absence, character, and duration of symptoms and by the nature of the inocula.

Rabbits and mice were inoculated either directly with suspensions in saline or with material obtained from nasopharynx, tonsils, or teeth; with the primary cultures in dextrose-brain broth, with suspensions of single colonies likewise from the end point of growth, or with dextrose-brain broth cultures of freshly isolated strains after a variable number of rapidly repeated subcultures in dextrose-brain broth. Intracerebral inoculations in all instances were made under ether anesthesia.

Routinely, two rabbits were inoculated intracerebrally, one with 0.1 ml., the other with 0.2 ml., of the saline suspensions or with like amounts of 1:200 to 1:10,000, or greater dilution, of the pure cultures of the streptococci in dextrose-brain broth. Mice at first were inoculated intracerebrally with 0.03 ml. of the suspensions and of 1:10 dilution of the pure cultures and intraperitoneally with 1.2 ml. of undiluted cultures. After it was found that largely negative results were obtained as regards the occurrence of characteristic symptoms, a larger number of streptococci was inoculated. Accordingly 0.03 ml. of 10:1 suspensions in sodium chloride solution of young dextrose-brain broth cultures, 20:1 suspensions of the heat-killed organisms, and 10 per cent emulsions of the brains of mice that had succumbed were inoculated intracerebrally, and 0.1 ml. of 20:1 suspensions of dextrose-brain broth cultures of the streptococci were inoculated intranasally. Filtrates of dextrose-brain broth cultures were injected intracerebrally and intravenously in sodium chloride solution in 0.03 ml. and 1 ml. amounts, respectively.

The animals were observed and symptoms recorded at frequent intervals during the day and at crucial points several times during the night. They were examined for lesions under a strong light as soon after death as possible, and cultures were made on blood agar plates and into dextrose-brain broth of brain substance admixed with

cerebrospinal fluid and from the blood from the heart. Pieces of the brain were placed in 10 per cent formalin for sections.

RESULTS OF CULTURES

Cultures on blood agar plates were made of nasopharyngeal swabbings from 181 persons suffering from epilepsy, from 258 persons suffering from schizophrenia, from 85 persons suffering from chronic or subacute arthritis, and as a control from 78 well persons. Green-producing colonies of alpha streptococci grew in predominating numbers in most instances and indifferent colonies grew in a few. Hemolytic or beta streptococci grew in a small number of instances and were never present in predominating numbers. Variable numbers of colonies of *Micrococcus catarrhalis* and staphylococci grew in most instances, and in one instance did *Hemophilus influenzae* grow in large numbers. There was no distinctive difference between the type of colonies that grew in the different groups. In general, however, the number of colonies was greater, often far greater, in the cultures from persons who were ill than was observed in comparable cultures from well persons.

SHAKE cultures in blood agar and serial dilution cultures in dextrose-brain broth or alternately in dextrose-brain broth and dextrose-brain agar were made from the spinal fluid in 24, from the urine in 10, from the apexes of pulpless teeth extracted in a sterile manner in 24, and from the stool in 23 persons suffering from schizophrenia. The spinal fluids proved sterile; greenish streptococci were isolated in small numbers from the urine and in large numbers from the teeth; and greenish or indifferent streptococci were isolated in 19 of the 23 stools cultured.

Cultures in the dextrose-brain broth of the partially macerated blood clot yielded highly pleomorphic greenish or indifferent streptococci to blood agar in 49, or 29 per cent, of 161 persons suffering from epilepsy, in only 5, or 4 per cent, of 125 persons suffering from schizophrenia, and in 7, or 14 per cent, of 69 persons having chronic arthritis; the cultures from 62 well persons or persons suffering from noninfectious ailments yielded nothing. The incidence of isolation of streptococci from the blood in persons having epilepsy was highest shortly before or during seizures, and most of the 49 persons from whose blood the streptococcus was isolated were taking phenobarbital or dilantin or both at the time the blood was drawn.

Agglutination tests were made with antisera prepared in horses and rabbits and with thermal antibodies prepared in vitro with streptococci isolated from nasopharynx or blood in studies of epilepsy, schizophrenia, and arthritis and with the respective sera on the streptococci isolated from the nasopharynx, teeth, blood, urine, and stool. Results of these studies and of the precipitation and intradermal tests with the respective antisera and thermal antibodies will be reported elsewhere. Suffice it to state here that evidence of respective specificity of the streptococci isolated from the nasopharynx, teeth, and blood was obtained by each of these methods, whereas the strains of streptococci isolated from urine and stool proved nonspecific.

RESULTS OF EXPERIMENTS IN MONKEYS

Convulsions and disorientation of mental processes sometimes occur during or following streptococcal or other infections. In order to determine the conditions under which streptococci and other causative agents may cause spasms or convulsions and disorientation, we reviewed the results of a large number of experiments in monkeys in which such symptoms sometime developed following inoculation of (1) natural or experimentally produced poliomyelitic and encephalitic virus, (2) streptococci isolated from these and from nasopharynx and spinal fluid of patients and monkeys that had succumbed to poliomyelitis, poliomyelitis, or encephalitis, and (3) of streptococci isolated from nature in relation to epidemics of poliomyelitis and encephalitis and in relation to non-epidemic diseases.

Of a total of 1,338 monkeys that were inoculated with cultures of streptococci or material containing streptococci during the years 1917 to 1944, spasms or convulsions were recorded to have occurred in 109, or 8 per cent, and symptoms simulating in certain respects those of schizophrenia in 24, or 1.8 per cent. Table 1 summarizes the incidence of spasms or convulsions that developed in the *Macacus* monkeys following inoculation of material containing streptococci in relation to poliomyelitis and encephalitis and the incidence of the demonstration in, or the isolation of, streptococci from spinal fluid or brain of animals in which spasms developed.*

It will be seen that the incidence of spasms or convulsions and the demonstration of streptococci in spinal fluid or brain in the monkeys in which spasms had developed, in general, paralleled the incidence of spasms or convulsions and the ease with which streptococci are demonstrable in the respective spontaneous diseases. Moreover, the incidence, severity, and duration of spasms of convulsions in the different groups of inoculated monkeys paralleled roughly the incidence of spasms which occur in spontaneous poliomyelitis, poliomyelitis, and encephalitis.

The drop in incidence of spasms from 26, or 54 per cent, of the 48 monkeys that received the experimental streptococcal virus while in the encephalitic phase to 3, or 6 per cent, of 51 monkeys that received the experimental virus in the poliomyelitic phase is especially noteworthy.^{40, 41, 42} Of 109 monkeys developing spasms, 36 of them received Berkefeld or Seitz filtrates of brain or cord emulsions of animals that had been inoculated with virus containing streptococci or with filtrates of chick embryo cultures of streptococci; 48 received emulsions of the brains of mice, rabbits, or monkeys that had been inoculated with natural or experimentally produced virus and from which streptococci were isolated; and 25 received cultures of neurotropic alpha streptococci in high dilution.

The onset of spasms ranged from two to sixteen days after inoculation in the different groups and averaged 5.2 days. In most instances the spasms resembled those obtained following inoculation of the streptococcus isolated

*The experiments on monkeys and on some of the rabbits were done at the Mayo Foundation for Medical Education and Research, Rochester, Minnesota, during the course of studies on the relation of the streptococcus to poliomyelitis and encephalitis and their respective viruses.

It is the purpose of this paper to describe the methods used, to record unpublished experiments on *Macacus rhesus* monkeys which had been inoculated with streptococci from diverse sources, and to report results obtained in a bacteriologic study of epilepsy and schizophrenia and of the localization in animals of the respective streptococci as isolated.

METHODS

Nasopharyngeal swabbings of patients suffering from various diseases, including epilepsy and schizophrenia, were made with aluminum-wire-wrapped swabs bent to a suitable angle so as not to touch the tongue. Pus from tonsils was expressed and scooped with a small bent laryngeal mirror. Purulent material from the depth of pyorrhea pockets was aspirated into capillary pipettes. Severed apices of pulpless teeth were extracted in a sterile manner. Each of these materials was suspended in 2 ml. of a 0.2 per cent gelatin-Locke or isotonic sodium chloride solution for cultures, precipitation tests, and inoculation of animals.

Cultures were made from spinal fluid, from the centrifuged sediment of freshly voided urine, and from suspensions of stool in sodium chloride solution. The surface of horse blood agar plates was inoculated routinely, and serial dilution cultures³⁹ were made in mediums affording a gradient of oxygen tension, usually alternately in dextrose-brain broth (0.2 per cent dextrose) and soft dextrose-brain agar (0.2 per cent dextrose and 0.2 per cent agar) in tall (12 cm.) columns in test tubes ($\frac{3}{8}$ x 6 or 8 inches). The dextrose-brain broth and dextrose-brain agar were usually freshly prepared by adding before autoclaving approximately 1 part by volume of pieces of fresh or frozen calf or young beef brain to approximately 7 volumes, or 15 ml., of the medium, previously adjusted to pH 7.2 and then autoclaved at 15 pounds pressure for twenty minutes.

The amount of inoculum in the first tube and the degree of serial dilution was determined roughly by the number and kind of organisms found in Gram-safranin stained films of the material under study. Serial, one hundredfold, dilutions or 10^{-2} of the materials suspended in sodium chloride solution were usually made by transferring 0.15 ml. from tube to tube with a 1 ml. pipette, and 10,000 fold or 10^{-4} dilutions of cultures were made by transferring 1.5 ml. from tube to tube with nichrome wire. The same pipette or wire was used for the serial dilutions without sterilizing between transfers. Hence, the successive dilutions represent dilutions of liquid and not necessarily corresponding dilutions of organisms.

Seven ml. of blood were routinely drawn from the vein at the bend of the elbow into sterile vacuum tubes. The blood was allowed to clot. The rubber stopper was then removed, in a sterile manner, the clot loosened with a sterile capillary pipette, the rubber stopper replaced, and the vial centrifuged. The serum was decanted then, and in a sterile manner, the partially macerated clot was transferred into 200 ml. of freshly prepared dextrose-brain broth. The small amount of blood remaining in the stoppered vial and the inoculated dextrose-brain broth were then incubated. Gramsafranin stained films were made

and examined for bacteria as soon as evidence of growth in the broth had occurred, and in five or seven days such films were made from the blood residue in the vial and from the sediment of seemingly negative cultures. All cultures were incubated at 33°C. to 35°C.

Pure cultures of the streptococci for inoculation of animals and other studies were obtained not from primary blood agar plates, but from the end point of growth of usually young primary serial dilution cultures alternately in dextrose-brain broth and dextrose-brain (agar or from young primary cultures in dextrose-brain) broth. Blood agar plates were made of these to determine the type of streptococcus and to check the purity of the cultures.

MONKEYS were inoculated intracerebrally usually with 1.5 ml. of the washings of nasopharyngeal swabbings of patients, of corresponding pure cultures in dextrose-brain broth or autoclaved chick embryo medium of the streptococci diluted 1:200 or more, and of emulsions or filtrates of emulsions of the brains and spinal cords of mice, rabbits, or monkeys that had succumbed to poliomyelitis, polio-encephalitis, or encephalitis following intracerebral inoculation. In some instances intraspinal, intravenous, and intramuscular inoculations were given in addition to intracerebral inoculations.

Inoculations were repeated at short or long intervals as indicated by the absence, character, and duration of symptoms and by the nature of the inocula.

Rabbits and mice were inoculated either directly with suspensions in saline or with material obtained from nasopharynx, tonsils, or teeth; with the primary cultures in dextrose-brain broth, with suspensions of single colonies likewise from the end point of growth, or with dextrose-brain broth cultures of freshly isolated strains after a variable number of rapidly repeated subcultures in dextrose-brain broth. Intracerebral inoculations in all instances were made under ether anesthesia.

Routinely, two rabbits were inoculated intracerebrally, one with 0.1 ml., the other with 0.2 ml., of the saline suspensions or with like amounts of 1:200 to 1:10,000, or greater dilution, of the pure cultures of the streptococci in dextrose-brain broth. Mice at first were inoculated intracerebrally with 0.03 ml. of the suspensions and of 1:10 dilution of the pure cultures and intraperitoneally with 1.2 ml. of undiluted cultures. After it was found that largely negative results were obtained as regards the occurrence of characteristic symptoms, a larger number of streptococci was inoculated. Accordingly 0.03 ml. of 10:1 suspensions in sodium chloride solution of young dextrose-brain broth cultures, 20:1 suspensions of the heat-killed organisms, and 10 per cent emulsions of the brains of mice that had succumbed were inoculated intracerebrally, and 0.1 ml. of 20:1 suspensions of dextrose-brain broth cultures of the streptococci were inoculated intranasally. Filtrates of dextrose-brain broth cultures were injected intracerebrally and intravenously in sodium chloride solution in 0.03 ml. and 1 ml. amounts, respectively.

The animals were observed and symptoms recorded at frequent intervals during the day and at crucial points several times during the night. They were examined for lesions under a strong light as soon after death as possible, and cultures were made on blood agar plates and into dextrose-brain broth of brain substance admixed with

second day, and one monkey was given 2 ml. intracerebrally and 3 ml. intraspinaly of a Berkefeld filtrate of 10 per cent emulsion of the brain of the monkey. The third rabbit developed symptoms similar to those shown by the two rabbits that received the sodium chloride solution suspension from the nasopharynx of the patient. The monkey remained free from symptoms for twenty days, when it became extremely excitable and repeatedly threatened to charge when observed unmolested in its cage. On being prodded it developed severe tremors and slight clonic spasms. The temperature was 106°F. The following day the temperature was 105.2°F. It continued to be extremely excitable, threatening to charge for several days; then it recovered gradually. It remained well for three months, when it was inoculated with material from another source.

EXPERIMENTS IN RABBITS WITH STREPTOCOCCI ISOLATED IN STUDIES OF EPILEPSY AND SCHIZOPHRENIA

The occurrence at times of spasms or convulsions and of disorientation in monkeys following inoculation of streptococci or material containing streptococci from diverse sources led to a study of the effects in rabbits of streptococci isolated in studies of epilepsy and schizophrenia. The results obtained in rabbits are summarized in Table 2. When rabbits were inoculated with the living cultures of the streptococcus, the dead bacteria, and filtrates of cultures from the nasopharynx and blood of persons suffering from epilepsy, the incidence of hyperirritability was far less, the incidence of tremors was about the same, and the incidence of spasms and convulsions was far greater than when they were given identical inoculations of the streptococcus isolated from the nasopharynx of persons suffering from schizophrenia. The mortality and isolations of streptococci from the brains of rabbits that succumbed was about the same in the two groups, but the isolations of streptococci from the blood following inoculation of the streptococcus from epilepsy was from three to five times as great in the different groups that received living streptococci as following inoculation of the streptococcus from schizophrenia.

The source and type of inocula, the number and type of streptococci, and the time of onset of symptoms were all comparable. But as symptoms progressed, a striking difference became apparent. Severe tremors and spasms of masseters, generalized tremors and ataxia, clonic and tonic spasms, and often recurring generalized convulsions resembling grand mal developed in rabbits that received the living or dead streptococci or the filtrate of cultures isolated from the nasopharynx or blood of persons suffering from epilepsy (Protocols 4 and 5). In sharp contrast extreme hyperirritability with evidence of disorientation usually without spasms developed in the rabbits inoculated with the streptococcus isolated from the nasopharynx of persons suffering from schizophrenia or manic-depressive psychosis (Protocol 6).

Symptoms characteristic of the disease in question usually developed in a large percentage of animals inoculated with the streptococcus of a given case, especially if cultures were obtained at the time of acute attacks. Myoclonic spasms developed in each of a group of rabbits inoculated respectively with the streptococcus isolated from the nasopharynx, blood, and an extracted pulpless tooth of

a man, a teacher who was becoming incapacitated because of recurring attacks of grand mal. Following the extraction of the tooth, his attacks of grand mal disappeared and had not recurred for nine years.

In sharp contrast, severe tremors and extreme hyperirritability sometimes accompanied by mild clonic spasms developed in each of 11 rabbits following intracerebral inoculation of a highly diluted culture of the streptococcus isolated, shortly after death, from the nasopharynx of a young woman who committed suicide by jumping from the top of a tall building during an acute attack of "psychoneurosis." The streptococcus inoculated was so far removed from the original source as to eliminate the possibility of the presence of virus.

RESULTS OF EXPERIMENTS IN MICE

At first mice were inoculated intracerebrally with 0.03 ml. of the sodium chloride solution suspension or with the primary young culture of the streptococcus undiluted or diluted 1:10 in sodium chloride solution of nasopharyngeal swabbings of persons suffering from epilepsy or schizophrenia. The results were considered as suggestive of specificity of the respective streptococci.

Thus, 8, or 18 per cent, of 43 mice that received the streptococcus from 35 persons suffering from epilepsy were seen to have severe tremors, twitchings, and mild clonic spasms, and 68, or 33 per cent, of 205 mice similarly inoculated with the streptococcus from the nasopharynx of 55 persons who were suffering from schizophrenia developed hyperirritability and, more rarely, catatonic states that were usually without spasms.

SINCE mice proved relatively resistant to the streptococcus, it was thought that if larger numbers of the streptococci were inoculated, especially streptococci obtained from the end point of growth in serial dilution cultures of dextrose-brain broth, a higher incidence of respective specific effects might be obtained. Accordingly, we inoculated intracerebrally 0.03 ml. of 10:1 suspensions in saline of dextrose-brain broth cultures and suspensions of similar density of the streptococci from streak cultures on blood agar plates made with the brains of mice that succumbed to inoculations.

In the experiments summarized in Table 3, two pooled suspensions of streptococci from cultures at the end point of growth of the nasopharyngeal swabbings—one from 13 and the other from 11 persons suffering from severe epilepsy—and corresponding cultures from each of 5 other persons having epilepsy, or seven suspensions in all, were inoculated into 17 mice in the first animal passage; 4 strains were used in the second passage; and then further animal passages were made with the strain derived from pooled cultures from the 11 cases. Spasms occurred in the mice following the inoculation of each of the suspensions of the different pools and strains. The cultures from the nasopharynx of well persons used as a control group were similarly pooled and similarly inoculated. Spasms developed in only 3 of 23 mice in the first passage, and in none of 21 mice in the second passage; hence, no further animal passage of control strains were done.

It will be seen that the incidence of spasms and convulsions following intracerebral inoculation of the living

TABLE 2

MORTALITY, SYMPTOMS AND SIGNS, AND ISOLATION OF STREPTOCOCCI FROM THE BRAIN AND BLOOD OF RABBITS FOLLOWING INTRACEREBRAL INOCULATION OF STREPTOCOCCI ISOLATED FROM PERSONS SUFFERING FROM EPILEPSY AND SCHIZOPHRENIA

SYMPTOMS OR FINDINGS IN PER CENT												
SOURCE OF STREPTOCOCCI	MATERIAL INJECTED OR INTRACEREBRALLY	STRAINS OR CASES	RABBITS		SYMPTOMS OR FINDINGS IN PER CENT					STREPTOCOCCI		
			IN-JECTED	PER CENT DIED	HYPER-IRRITABILITY	TREMORS	SPASMS	CONVULSIONS	BRAIN		BLOOD	
									CULTURED	PER CENT	CULTURED	PER CENT
EPILEPSY (46 Cases)	Suspension of material directly from nasopharynx, tonsils, or teeth	37	72	65	29	75	75	33	47	94	46	26
	Dextrose-brain broth cultures from nasopharynx, tonsils, teeth, or blood diluted 1:200 to 1:10,000	26	34	91	15	74	73	35	25	92	23	43
	Total for material containing living streptococci	63	106	74	25	75	75	34	72	93	69	32
	Heat killed streptococci and filtrates of dextrose-brain broth cultures	10	19	58	11	74	79	47	11	0	6	0
SCHIZOPHRENIA (45 Cases)	Suspensions of material directly from nasopharynx or dextrose-brain broth cultures diluted 1:200 to 1:10,000	45	77	87	87	79	21	3	54	83	46	7

streptococcus obtained from persons suffering from epilepsy was remarkably high throughout nine successive passages, averaging 93 per cent and 69 per cent, respectively, and that spasms and convulsions almost never occurred in control mice inoculated in identical manner with the streptococcus isolated from the control group of well persons. The incidence of spasms and convulsions following inoculation of suspensions of the heat-killed streptococci and filtrates of dextrose-brain broth cultures of streptococci isolated from persons having epilepsy was also high, whereas no spasms developed in mice that received suspensions and filtrates from the control group.

The statistical evidence of specificity shown in Table 3, though striking, does not express adequately the specific character and type of symptoms that developed in these mice following inoculation of the living and the heat-killed streptococcus and filtrates of cultures.

The mice usually remained apparently well for from four to twelve, and sometimes for twenty-four, hours after inoculation. Evidence of illness was first manifested by their becoming abnormally quiet and standing humped up with roughened fur and by increased respiration and fine and coarse tremors; these were followed somewhat later by hyperirritability, and then in rapid succession by scratching of the nose or side of the head, severe tremors, twitching, and clonic spasms of muscles of the face, ears, neck, and extremities. They then fell to the side as the head was pulled violently to one side or other or backward, as generalized tonic followed by clonic spasms and often voiding of urine occurred. These symptoms were followed in turn by increased respiration as they lay relaxed, apparently unconscious and insensitive for a moment to stimuli or proddings. Recovery often appeared

to be complete as symptoms developed soon after inoculation, but as symptoms became worse hour by hour or day by day, the spasms and convulsions were almost continuous, and in most instances the mice died apparently from exhaustion during seizures resembling "status epilepticus."

OF THE 130 mice inoculated with the streptococcus from the nasopharynx of persons suffering from severe epilepsy, 102, or 78 per cent, died in from one to eight days. Spasms did not occur at all in 12 of the 28 that survived, and the recurring seizures in the remaining 16 disappeared during the course of two weeks.

Of the 44 mice inoculated with the streptococcus from the nasopharynx of well persons used as a control, 12, or 27 per cent, died. Seven of these died within twenty-four hours, and 5 died on the second day after inoculation.

The tendency of the strains from persons having epilepsy to produce spasms and convulsions when grown in dextrose-brain broth persisted through consecutive serial dilution cultures representing dilutions of original inoculum of at least 10^{-10} to 10^{-80} , and as shown in Table 3, persisted through nine consecutive passages through mice following inoculation of brain emulsions, primary cultures, and of from three to five subcultures rapidly repeated. The spasm-producing property was found to be present in undiminished form in one strain that had been passed through six series of mice on isolation after it was kept at room temperature dried on glass balls in vacuo under a desiccant and on a sealed blood agar slant for three weeks and after seven rapidly repeated (two or three per day) subcultures in dextrose-brain broth. It was

then subcultured in dextrose-brain broth every third or fourth day for five additional subcultures, whereupon it had not only lost the power to produce spasms but apparently all virulence, since spasms did not develop in any of the 10 mice, 2 rabbits, and 2 rats inoculated, and all animals survived.

Having found a fairly precise method for measuring symptom-producing and localizing power of streptococci in mice, we studied the comparative effect on mice of the intracerebral and intranasal inoculation of streptococci isolated from the nasopharynx of persons suffering from different types of epilepsy, persons suffering from dementia paralytica with and without convulsions, of well persons; and also the inoculation of streptococci isolated from the brain of an uninoculated baby mouse that died in convulsions, and of streptococci isolated from poliomyelitic virus virulent for monkey and mice.*

The mother of the baby mouse that was seen to die in spasms had been inoculated intranasally several times, in the early stages of gestation, with the streptococcus from a person suffering from grand mal epilepsy in the seventh mouse passage. No symptoms were noted either in the mother mouse or in the three litter mates which grew to maturity without spasms or convulsions.

The streptococci from the end point of growth of the usual serial dilution cultures were inoculated intracerebrally under ether anesthesia in the usual and comparable

dosage for the different strains. Intranasal inoculations were made under deep ether anesthesia with 20:1 suspensions in sodium chloride solution of the respective streptococci. These were usually repeated once or twice daily for three or four times. An attempt was made to lower the inherently high resistance of the brain to invasion of noxious agents, by injecting 0.03 ml. of sterile sodium chloride solution intracerebrally just before or after the first intranasal inoculation in alternate mice and in control mice. No symptoms developed in the latter group. The number of "takes" in mice that received sodium chloride solution intracerebrally and the streptococcus intranasally was approximately twice as great as in those that received only intranasal inoculations. The results in this series of experiments are summarized in Table 4.

It will be seen that (1) the incidence of spasms and convulsions was uniformly much higher in mice that received intracerebral inoculations of the streptococci isolated from conditions characterized by spasms or convulsions (epilepsy, dementia paralytica, and the mouse with convulsions)—spasms occurred in 81, or 88 per cent, and generalized convulsions in 64, or 70 per cent, of 92 mice so inoculated—than in those that received inoculations from conditions in which spasms or convulsions were absent—spasms occurring in 10, or 11 per cent, and convulsions in 2, or 2 per cent, of 89 mice so inoculated; (2) spasms and convulsions occurred in significant incidence following intranasal inoculation of the streptococci isolated in studies of each of the three types of epilepsy; (3) paralysis occurred in 24, or 45 per cent, of 53 mice that

TABLE 3
RESULTS IN MICE FOLLOWING INTRACEREBRAL INOCULATION OF STREPTOCOCCI ISOLATED FROM THE NASOPHARYNX OF PERSONS SUFFERING FROM IDIOPATHIC EPILEPSY AND FROM WELL CONTROLS

SOURCE OF STREPTOCOCCI	ANIMAL PASSAGE	STRAINS OR CASES	INOCULATED	MICE				STREPTOCOCCUS FROM	
				SEEN TO HAVE		DIED	CULTURED	BRAIN	BLOOD
				SPASMS	CONVULSIONS				
NASOPHARYNX OF PERSONS SUFFERING FROM IDIOPATHIC EPILEPSY	1	29	17	16	10	20	11	11	6
	2	4	18	16	11	14	10	10	5
	3	1	9	9	7	8	7	5	2
	4	1	6	5	3	7	4	4	2
	5	1	39	38	33	27	24	25	18
	6	1	14	14	11	11	10	9	7
	7	1	15	12	9	10	5	4	3
	8	1	8	8	4	7	7	7	7
	9	1	4	3	2	3	3	3	1
TOTAL	1-9	30	130	121 (93%)	90 (69%)	107 (82%)	81	78 (98%)	51 (63%)
NASOPHARYNX OF CONTROL WELL PERSONS	1	32	23	3	1	9	8	7	4
	2	8	21	0	0	3	1	1	1
TOTAL	1-2	32	44	3 (7%)	1 (2%)	12 (28%)	9	8 (89%)	5 (56%)
EPILEPSY	Heat killed streptococci	4	15	11 (73%)	9 (60%)	8 (53%)	8	0	0
CONTROL		4	12	0	0	0	0	0	0
EPILEPSY	Filtrate of cultures of streptococci	6	22	11 (50%)	4 (18%)	2 (9%)	4	0	0
CONTROL		5	10	0	0	0	0	0	0
	Filtrate of uninoculated broth	5	10	0	0	0	0	0	0

*I am indebted to Dr. C. A. Armstrong, Washington, D. C., for the poliomyelitic virus virulent for monkey and for the Lansing strain of virus adapted to the mouse and to C. W. Jungblut, New York, for two strains of murine poliomyelitic virus.

TABLE 4

RESULTS IN MICE FOLLOWING INOCULATION OF STREPTOCOCCI ISOLATED FROM THE NASOPHARYNX OF PERSONS SUFFERING FROM DIFFERENT TYPES OF EPILEPSY, OF WELL PERSONS AND OF PERSONS SUFFERING FROM DEMENTIA PARALYTICA WITH AND WITHOUT CONVULSIONS, FROM THE BRAIN OF A BABY MOUSE THAT DIED IN CONVULSIONS, AND FROM THE BRAIN AND SPINAL CORD OF MONKEY AND MICE THAT HAD SUCCEEDED TO "VIRUS" POLIOMYELITIS.

SOURCE OF STREPTOCOCCI	ANIMAL PASSAGE	STRAINS OR CASES	INOCU- LATION	INOCU- LATED	MICE					STREPTO- COCCI FROM BRAIN
					SEEN TO HAVE		PARAL- YSIS	DIED	CUL- TURED	
					SPASMS	CONVUL- SIONS				
"GRAND MAL" EPILEPSY	6 and 7	1	Cerebral	20	16	12	0	15	9	8
			Nasal	11	6	3	0	3	3	2
"GRAND MAL" EPILEPSY	1 and 2	1	Cerebral	8	8	7	0	8	3	3
			Nasal	11	5	1	0	2	1	0
"PETIT MAL" EPILEPSY	1 and 2	1	Cerebral	9	9	7	0	7	7	6
			Nasal	17	5	3	0	3	3	0
MENTALLY DETERIORATED EPILEPTIC	1 and 2	1	Cerebral	14	11	10	0	11	8	5
			Nasal	11	6	2	0	1	1	0
TOTAL FOR CASES OF EPILEPSY	1, 2, 6, and 7	4	Cerebral	51	44	36	0	41	27	22
			Nasal	50	22	9	0	9	8	2
DEMENTIA With convulsions	1 and 2	6		19	18	12	0	12	5	5
PARALYTICA Without convulsions	1	6		18	3	1	0	14	5	5
CONTROL, WELL PERSONS	1	6	Cerebral	18	3	0	0	11	6	6
BABY MOUSE (9 GRAMS) THAT DIED IN CONVULSIONS	1 and 2	1		22	19	16	0	17	11	10
POLIOMYELITIC VIRUS	1 to 5	4		53	4	1	24	36	25	21

were inoculated with the four strains of streptococci isolated from the brain and spinal cord of a monkey and of mice that died of poliomyelitis following inoculation of virus; this paralysis did not occur in any of 110 mice similarly inoculated with streptococci from sources in which paralysis was absent; and (4) cultures of the brain of 8 mice that developed spasms and that died following intranasal inoculation of the streptococcus from epileptics yielded the streptococcus in only two instances, indicating that the spasms were due perhaps to the absorption of specific neurotoxin from the nasopharynx and from the site of inoculation; the streptococcus was isolated from these areas after death in each instance.

Frothing at the mouth during convulsive seizures was not observed in either mice or rabbits, but sometimes occurred in monkeys during severe convulsive seizures resembling grand mal. Symptoms resembling petit mal and psychic seizures of epilepsy seemingly occurred in mice, rabbits, and monkeys after they were inoculated with the living and heat-killed streptococcus isolated from nasopharynx and blood of persons suffering from epilepsy.

The brain after death in monkeys and rabbits that had succumbed during acute symptoms and in mice that died after spasms had disappeared usually revealed severe congestion, whereas the brain, especially the cerebral cortex, of the mice that succumbed during "status epilepticus" was ischemic, edematous, and usually showed severe cloudy swelling. In no instance was there hemorrhage or abscess formation at the site of inoculation, and grossly visible meningitis was seen in only one mouse in which cultures revealed contamination with *E. coli*. There were no noteworthy lesions of the viscera.

Sections of the brains of monkeys, rabbits, and mice

stained by hematoxylin and eosin, by the Morgan iron hematoxylin method, and for bacteria by a modification of the Gram-Weigert method in which decolorization with alcohol was carried only to a fair blue instead of to the end point, have been examined for lesions and for bacteria.

THOSE from animals that received inoculations of streptococci isolated in studies of schizophrenia showed only slight or moderate congestion of meninges and cerebral cortex and only slight, widely scattered areas of cellular infiltration. Those from monkeys and rabbits that had been inoculated with streptococci isolated in studies of epilepsy revealed marked congestion and moderate infiltration by leukocytes of meninges in sulci and in superficial layers of the cortex. Sections of the brain of mice that were inoculated with the streptococci from epileptics revealed only slight infiltration of the meninges and the superficial layers of the cerebral cortex, but showed moderate infiltration of the subcortex and severe infiltrations by leukocytes surrounding the choroid plexus and in localized areas of necrosis in the walls of the ventricles. Large numbers of streptococci, chiefly within leukocytes, were found in sections of the brain of animals that died in "status epilepticus" soon after inoculation of streptococci, and only a few or none were demonstrable in animals that died or were anesthetized long after inoculation of living cultures or that died of spasms soon after inoculation of filtrates of cultures. Perivascular infiltration by lymphocytes characteristic of encephalitis was not found regardless of the species of animal or the duration of experiment following inoculation.

The occurrence of maximal lesions, including necrosis, in the walls of the cerebral ventricles in the brain of mice that succumbed to epileptiform seizures following inoculation of the streptococcus isolated from the nasopharynx or blood of persons suffering from epilepsy are in accord with the changes found in the region of the tuber cinereum in the brain of persons suffering from idiopathic epilepsy by Morgan⁴⁴ and by Morgan and Gregory⁴⁵ and those induced by Morgan and Johnson⁴⁶ in the tuber cinereum in the brain of dogs in which epileptiform seizures developed.

ILLUSTRATIVE PROTOCOLS

Protocol 1—A small *Macacus rhesus* monkey was inoculated intracerebrally in the right frontal lobe January 7, 1935, with 1.5 ml. of the emulsion of the brain of a mouse that had succumbed to symptoms of poliomyelitis after inoculation of a streptococcus isolated from a water supply of a case of poliomyelitis. The streptococcus, before inoculation into the mouse, was in the tenth rapidly repeated subculture in dextrose-brain broth. Cultures from emulsions of the brain yielded a pure growth of alpha streptococci.

January 9: The animal was excitable, ataxic, and tremulous, and had diminution of vision. The pupils were dilated, and there was slight weakness of the left fore extremity. The condition remained about the same for nine days, when a violent generalized convulsion occurred in which the animal lost its balance, voided urine, and lay unconscious for five minutes; consciousness gradually returned and the animal appeared to be recovered.

February 13: Twenty-six days after inoculation, the monkey was anesthetized and inoculated intracerebrally with 2 ml. of a 10 per cent emulsion of the brains of 3 mice that had succumbed with symptoms of encephalitis after being inoculated with an experimental streptococcal virus strain while in the encephalitic phase.⁴⁰

February 15: The animal was very excitable, ataxic, and tremulous. Its vision was impaired. There was partial paralysis of the right fore and hind extremities. There was little change in the animal's condition until March 5, when it again had a severe generalized convulsion with urination and loss of consciousness resembling a grand mal seizure.

March 6: The monkey was excitable and ataxic; it missed its mark badly on jumping out of and into its cage because of blurred vision and incoordination. It had another violent epileptiform seizure with generalized tonic spasms followed by clonic spasms, frothing at the mouth, urination, and unconsciousness.

March 9: The animal repeatedly had spells apparently of momentary loss of consciousness, in which it sometimes fell to the floor without spasms; these spells resembled petit mal.

March 10 and 11: Ataxia and hyperirritability continued, resembling grand and petit mal.

March 12: The monkey was reinoculated with the emulsion of the brains of 2 mice that had succumbed to two further passages of the same virus diluted three hundredfold in sodium chloride solution.

March 13: The animal was ataxic and hyperirritable, and on jumping from its cage it had a severe generalized convulsion resembling grand mal.

March 18: The animal seemed better, and no convulsions were noted for eleven days.

March 29: The animal was inoculated with a 50 per cent emulsion diluted one thousandfold of the brains of 2 other mice that had succumbed to further successive passages of the experimental virus. The animal remained about the same, and no spasms were noted until April 8, at which time a violent seizure occurred.

April 9: The monkey was less irritable; however, it missed its mark badly in jumping out of and into its cage, and when observed in its cage it had "lapses" resembling petit mal.

April 12: There was a recurrence of hyperirritability. The animal was more ataxic; generalized spasms did not occur, but it had severe tremors of its head associated with mild clonic spasms. The temperature was 104.8°F.

April 13: There was now great weakness of hind extremities and ptosis of the eyelids; the temperature was 103.4°F.

April 14: The tremors continued, but no spasms were noted. The animal was lethargic, and great weakness of hind extremities had developed. The temperature was 99°F.

April 15: The extremities were spastic, and they were so weak that the animal could not stand.

April 16: Condition was about the same, but on prodding mild generalized spasms developed. The temperature was 98°F. The animal was anesthetized to death with ether. There was moderate congestion of the cerebral cortex. The cerebrospinal fluid was greatly increased in amount but was clear. The cerebral ventricles were dilated. There was a small cyst at the site of intracerebral inoculation. Cultures from the pipetting of the brain proved sterile.

Protocol 2—A medium-sized *Macacus rhesus* monkey was inoculated intracerebrally December 20, 1936, with 1 ml. of a 1:200 dilution of a dextrose-brain broth culture of a streptococcus isolated from the blood of a patient who suffered from nocturnal epilepsy.

The animal remained well until December 25, when severe tremors and weakness of the hind extremities developed.

December 26: The animal had recurring seizures of generalized tonic and clonic spasms in which it lost its balance and fell to the floor; in severe seizures it voided urine, sometimes frothed at the mouth, and became unconscious for five minutes or more after which consciousness returned, and spasms disappeared. The attacks of spasms occurred at frequent intervals but in progressively milder form for ten days; they then disappeared as the animal recovered. It was observed until January 29, 1937, and no additional spasms were noted.

Protocol 3—A medium-sized *Macacus rhesus* monkey was inoculated May 20, 1935, with the Berkeley filtrate of a 5 per cent emulsion of the brain and spinal cord of a monkey that had succumbed to an intracerebral inoculation of experimental virus derived from a hemolytic streptococcus originally isolated from a case of endocarditis and which had been changed into an alpha streptococcus having neurotropic cataphoretic velocity and virulence and from which a filtrable virus was produced.⁴⁰ The experimental virus used for inoculation had been passed consecutively through 8 series of mice nearly all of which developed encephalitis. Cultures from the filtrate inoculated proved sterile. The monkey's temperature was 101°F. Of the filtrate 1.5 ml. was injected intracerebrally, 2 ml. intraspinally, 10 ml. intravenously, and 10 ml. intraperitoneally.

May 23: Cultures from the spinal fluid obtained at the time of inoculation were sterile. Gram-safranin stains of the centrifuged sediment of the spinal fluid revealed lymphocytes and a few gram-positive diplococci, and a short-chained streptococcus was isolated in dextrose-brain broth. The animal was fussy, and its temperature was 104°F. The injections were repeated.

May 24: The animal was hyperirritable, and the face was flushed. The temperature was 104.6°F.

May 26: The animal appeared abnormally quiet and half-dazed. The temperature was 101.6°F.

May 27: The animal acted strangely and kept looking to the right seemingly at imaginary objects; when prodded it suddenly seemed to realize its surroundings and became excitable and tremulous after which its strange action returned. Spinal puncture revealed slightly turbid spinal fluid due to lymphocytes, and in the centrifuged stained sediment a few unmistakable gram-positive diplococci were found. The temperature was 104°F.

May 28: 8 A.M.—Most of the time the animal did not seem to realize what was going on and still kept looking wildly about at imaginary objects. 6 P.M.—The animal was semicoma-

tose, in a generally rigid state resembling catalepsy, and had developed marked weakness, especially of the fore extremities. Respirations were slow, and heart action was very rapid. The temperature was 100.8°F. Spinal puncture revealed clear fluid and no bacteria.

May 29: Cataleptic symptoms were less marked. The animal lay on its side alternately in relaxed and rigid states. There was continual vertical nystagmus and marked drooling of saliva. It had repeated mild generalized clonic spasms in which the animal opened its mouth widely as spasms of the muscles of the jaw and tongue occurred. The animal was anesthetized to death. There was severe congestion of the brain; a small cyst was found in the right frontal lobe at the point of intracerebral injection. Cultures from pipettings of brain substance admixed with spinal fluid proved sterile. Sections of the brain revealed mild perivascular and parenchymatous round cell infiltration.

Protocol 4—A large rabbit weighing 2,850 gm. was inoculated intracerebrally January 27, 1936, with 1 ml. of the saline suspension of the nasopharyngeal swabbing of a patient suffering from severe epileptic seizures.

January 28: 8 A.M.—Tremors of masseters and mild clonic spasms of the muscles of the face and ears were noted. 9 P.M.—The animal was ataxic, respirations were greatly increased, weakness of hind extremities had developed, and mild generalized clonic spasms occurred at intervals.

January 29: 8 A.M.—The tremors were more marked and clonic spasms occurred frequently. 11:30 A.M.—A generalized spasm resembling grand mal occurred. 2 P.M.—While being watched, the animal suddenly leaped forward, fell to its side in violent tonic spasm followed by severe generalized clonic spasms. It voided urine and then lay unconscious with stertorous respiration for a short time. During this period it did not respond to stimuli. As consciousness returned, the animal rose to its feet; it was then free from spasms for two hours, when suddenly a similar but more violent seizure occurred, during which it died in generalized tonic spasms from respiratory failure. Necropsy revealed severe congestion of the brain, slight clouding of meninges, no mark at the site of intracerebral injection, and no lesions of the viscera. The streptococcus was isolated from the brain. The blood proved sterile.

Protocol 5—A white rabbit weighing 2,000 gm. was inoculated intracerebrally June 1, 1935, at 10 A.M. with 0.5 ml. of a sodium chloride solution suspension of the heat-killed streptococcus isolated from the nasopharynx of a patient suffering from severe epilepsy. At 2 P.M. and 5 P.M. marked tremors of masseters were elicited by palpation. At 8 P.M. the animal, while sitting quietly in cage, suddenly cried out as it developed a violent convulsive seizure. Spasms were tonic at first, then clonic as it apparently lost consciousness and stertorous, extremely irregular respiration developed. Shortly following this the animal regained consciousness and was again free from spasms; tremors of masseters continued, however.

June 2: 9 A.M.—The respirations were rapid; the animal was ataxic and tremulous, and tremors of masseters continued. 12 M.—The animal again developed a violent convulsion and died of respiratory failure with head retracted and extremities rigidly outstretched. Necropsy revealed severe congestion of the cerebral cortex and no mark at the site of injection. Cultures from brain and blood were sterile.

Protocol 6—A white and gray rabbit weighing 2,000 gm. was inoculated intracerebrally August 28, 1936, with 0.1 ml. of a culture of the streptococcus in autoclaved chick embryo medium isolated from the nasopharynx of a patient suffering from manic-depressive psychosis.

August 29, 30, and 31: The animal was extremely excitable and tremulous. It apparently imagined that it was about to be attacked since it repeatedly jumped violently about in its cage, and unknowingly jumped out of the cage when the door was opened. During quiet intervals the waving of one's hand over its body caused it to jump violently about.

September 1: The animal was greatly improved. It was

anesthetized with ether and reinoculated. Following this inoculation, it again became hyperirritable and instead of being frightened by imaginary objects it became extremely cross and it repeatedly threatened to charge.

September 3: The injection was repeated. The symptoms persisted, and the animal was found dead September 5. Necropsy revealed moderate congestion of the brain, no meningitis, no mark at the site of intracerebral inoculation, and no lesions of the viscera. The streptococcus was isolated from the brain in dextrose-brain broth. The blood proved sterile.

Protocol 7—A white mouse weighing 30 gm. was inoculated intracerebrally June 6, 1946, at 8 A.M. with 0.03 ml. of a 10:1 sodium chloride solution suspension of a streptococcus from a dextrose-brain broth culture of the nasopharynx of a patient suffering from idiopathic epilepsy and from the brain of a mouse that had succumbed to convulsive seizures following inoculation of this strain in the fifth mouse passage. The streptococcus before inoculation into the mouse was derived from growth in extremely high dilution and was in the second subculture. At 8 P.M. slight tremors had developed and respirations increased. At 9:35 P.M. its fur was ruffled and tremors were more pronounced. While it was being observed, recurring tonic and clonic spasms developed, beginning in the face and jaws and extending rapidly to the right foreleg and right hindleg. These were followed by generalized spasms in which the animal fell to the left, then turned on its back while having sharp clonic spasms of the muscles of the jaw and neck, and pulling its head sharply to the right and voiding urine. Following this, it lay limp, insensible to stimuli for fifteen seconds, when spasms recurred. It was observed continuously for one hour, during which time it had severe recurrences of tonic and clonic spasms resembling "status epilepticus."

June 7: 4 A.M. and 7 A.M.—Attacks of spasms recurred at short intervals but were less severe. Mild attacks of spasms continued through June 12, and the animal was found dead June 13.

The characteristic cloudy swelling and ischemia of brain was found at necropsy. The meninges were wet and shiny. There was no mark at the point of injection. The viscera were normal. Cultures of the brain were negative on blood agar but yielded the streptococcus in dextrose-brain broth. The blood proved sterile.

Protocol 8—A white mouse weighing 25 gm. was inoculated intracerebrally June 11 and 12, 1946, at 9 A.M. with 0.03 ml. of a 20:1 suspension in sodium chloride solution of the heat-killed streptococcus isolated from the brain of a mouse inoculated with the strain isolated from persons having epilepsy in the seventh mouse passage.

June 12: 9:30 P.M.—Severe tremors and slight spasms had developed. 10:30 P.M.—The animal had a generalized convulsion.

June 13: 4 A.M. to 10 A.M.—The animal was seen to have almost continuous tonic and clonic spasms resembling "status epilepticus," and at 11:45 A.M. the animal died during a severe seizure. Necropsy revealed moderate cloudy swelling of brain, but there were no other lesions. Cultures of brain and blood proved sterile.

Protocol 9—A white mouse weighing 30 gm. was inoculated intravenously June 3, 1946, with 0.5 ml. and intracerebrally with 0.03 ml. of a filtrate of a dextrose-brain broth culture of the streptococcus from the end point of growth of a serial dilution culture from the nasopharynx of a patient suffering from severe epilepsy.

June 4: 4:30 A.M.—The animal seemed well and was free from spasms. 10 A.M.—As animal was observed, undisturbed, it suddenly developed violent tonic and then clonic generalized convulsions lasting for about fifteen seconds. It then lay quietly, insensible to stimuli for about ten seconds, when it suddenly became rigid with severe tonic and then clonic spasms. It again lay quietly on its side, breathing violently for a few seconds, insensible to stimuli when a third similar seizure resembling

"status epilepticus" occurred, in which it died. Moderate congestion of the cerebral cortex was found at necropsy. Cultures of brain and blood proved sterile.

Protocol 19—A white mouse weighing 25 gm. was inoculated intranasally on June 18, 19, and 20, 1946, with 0.1 ml. of a 20:1 suspension of the live streptococcus after six animal passages and originally isolated from the nasopharynx of persons suffering from severe epilepsy. In addition, it was inoculated intracerebrally with 0.03 ml. of sterile sodium chloride solution immediately after the first intranasal inoculation.

June 21: Until this time the animal remained seemingly well. 7:15 A.M.—At this time of the day after the third intranasal inoculation, it was seen to have violent generalized tonic and then clonic spasms, in which the animal was thrown violently about as the head was drawn sharply backward and as extremities were outstretched in tonic spasms. This attack was followed shortly by rapidly recurring clonic spasms, grinding of teeth, and voiding of urine. The animal then lay limp, insensible to stimuli for ten seconds, when slight and later violent spasms occurred. Seizures resembling the one described then recurred in rapid succession for two hours, after which spasms became continuous resembling "status epilepticus" in which the animal died four hours later. There was slight congestion and cloudy swelling of the brain; the lungs and other viscera were normal. Cultures on blood agar from brain and blood proved sterile, and cultures from the brain in dextrose-brain broth yielded a pure culture of streptococcus.

COMMENTS AND SUMMARY

The occurrence of spasms or convulsions and of disorientation in monkeys in low incidence following inoculation of natural and experimental poliomyelitic and of encephalitic virus and neurotropic streptococci isolated from these and other sources, and the production of respective, more or less characteristic, symptoms in a high incidence in monkeys, rabbits and mice with alpha streptococci isolated from nasopharynx or blood of persons suffering from epilepsy and schizophrenia is reported.

The seizures, especially in mice following inoculation of the streptococci isolated from nasopharynx or blood of persons suffering from epilepsy, resembled those that occur spontaneously in patients in the periodicity, in the suddenness of onset of recurring seizures, in the rapid increment of spasms during attacks ending often in generalized convulsions, a falling to the side, voiding of urine, loss of consciousness, and rapidity of apparent recovery from recurring attacks.

Spasms and convulsions occurred in mice in about equally high incidence on intracerebral, and in comparable low incidence on intranasal, inoculation of the streptococci isolated from nasopharynx of persons suffering from different types of epilepsy—grand mal, petit mal, and psychomotor seizures with mental deterioration without convulsions—but due to prior seizures typical of epilepsy, and from epileptics in whom seizures were controlled by the administration of anticonvulsant drugs—phenobarbital or dilantin or both.

The symptoms in animals that followed the inoculation of the streptococcus isolated from persons suffering from idiopathic epilepsy and dementia paralytica were obviously more convincing proof of etiologic relationship than those following inoculation of the streptococci isolated from persons suffering from schizophrenia.

The occurrence of spasms and convulsions in the baby mouse shown to be due to the streptococcus whose mother had been inoculated intranasally early during gestation

with the streptococcus from an epileptic should not be interpreted as indicating either an in utero transmission of the streptococcus or an inherited predisposition, but should rather be interpreted as due to chance nasal-to-nasal infection after birth.

The data obtained indicate that persons suffering from idiopathic epilepsy and schizophrenia harbor in their nasopharynx and sometimes in their blood respective specific types of alpha streptococci, and that the symptoms characteristic of these diseases may be due in large part to the absorption of respective specific neurotoxic substances produced by the streptococci in nasopharynx or other areas of infection in addition to the localization and infection in the brain by the respective streptococci.

The negative cultures from the brain of animals that died from convulsive seizures resembling "status epilepticus" long after intracerebral or intranasal inoculation of the streptococci, the sharp drop of streptococcal antigen in skin or blood with concomitant sharp rise of specific antibody and transient disappearance of symptoms in patients following grand mal seizures, and the subsequent day-by-day increase of antigen (to be reported elsewhere) support the view generally held that the seizures and other symptoms in epilepsy are of toxic origin and that the streptococcus which we have isolated may be a common source of the specific neurotoxin.

A week or ten days after intracerebral, and especially after intranasal, inoculation of material containing the respective specific types of streptococci and negative cultures from the brain of persons for which the "neurotoxin" and the respective specific types of streptococci have predilection or elective affinity, animals may become sensitized so that extremely small amounts of the "neurotoxin"—too small to be detected in serum or blood—and small numbers of streptococci suffice to produce the respective characteristic symptoms.

The common occurrence of the respective specific types of streptococci in the blood of epileptics, especially shortly before or during grand mal seizures, and their occasional presence in the blood of persons suffering from severe schizophrenia are in accord with this idea.

The importance of heredity in relation to the presence of specific types of streptococci in epilepsy and schizophrenia, their relation to the electroencephalogram,⁴³ the nature of the respective streptococcal "neurotoxins," and active and passive immunization with specific streptococcal vaccines and thermal antibodies^{44, 45} are under study.

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Book of the Month—A Report

INTERNAL MEDICINE in GENERAL PRACTICE*

IN this relatively small volume, the basic principles and the practical considerations of the everyday problems in internal medicine are clearly and briefly reviewed. Quick reference with sensible application for the busy physician are two main functions of the text.

Controversial material and lengthy discussions of diseases rarely encountered are omitted, while diagnostic and therapeutic methods most readily adaptable for use in general practice have been stressed by the author.

An appropriate bibliography is included for those who wish more extensive detailed reading. Liberal use is made of illustrations, and many tables and charts are included in order to emphasize and simplify various topics.

Accurate diagnosis early in disease is a point the author repeatedly emphasizes when discussing the fundamentals of diagnosis in the first portion of the book. The author includes laboratory aids and new diagnostic technics, but cautions that these facilities are not substitutes for good clinical judgment based on a careful history and a thorough physical examination.

In view of the recent popularity of psychosomatic medicine, especially since World War II, a chapter on psychiatric disorders is included in this edition. Dr. McCombs feels that every physician should understand and know the manifestations of the more common psychiatric disorders, so that he can correct or forestall a large portion of these disorders by treatment which is often quite surprisingly simple.

*Internal Medicine in General Practice. By Robert Pratt McCombs, B.S., M.D., F.A.C.P., Professor of Medicine and Director of Postgraduate Teaching, Tufts College Medical School; Senior Attending Physician, The Joseph H. Pratt Diagnostic Hospital; Diplomate of the American Board of Internal Medicine. 697 pages, with 122 illustrations and 15 tables. Philadelphia, W. B. Saunders, Company, 1947.

The author emphasizes systematic methods of examination for any disease encountered, giving analyses of the many associated signs and symptoms, and discussing both their anatomic and physiologic interpretations.

No book of medicine is of practical value unless maximum consideration is given to therapy. In this text, Dr. McCombs reviews in detail the different therapeutic approaches: restriction of activity, dietary management, the use of drugs, etc., are all discussed at length. Not only "time tested" technics, but also the recent advances in therapy are included, as well as those little "common sense suggestions" which are usually learned only through years of experience.

The subject of peptic ulcer is given considerable attention since it is one of the most common diseases of the digestive tract, while another type of great interest which is given lucid explanation is the study of the liver and related diseases.

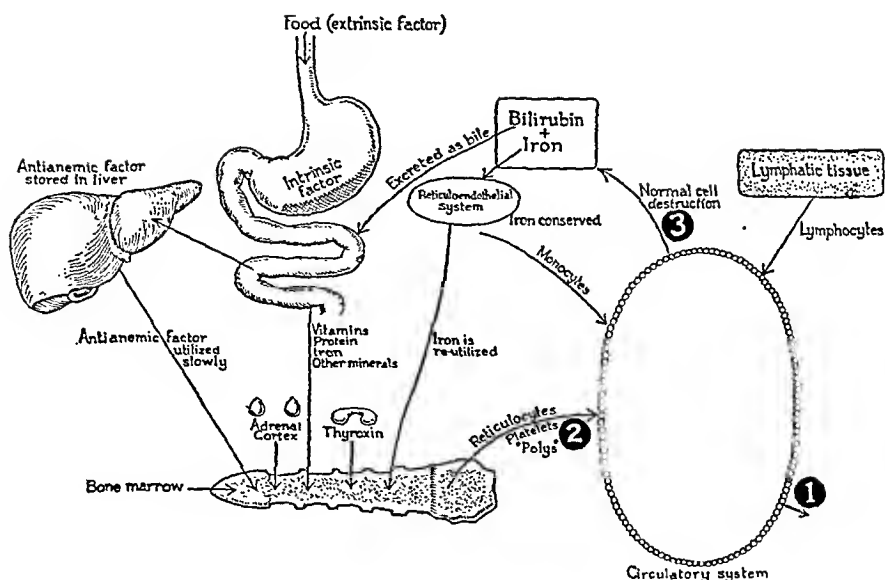
Immediately following the intestinal disorders are chapters on nutritional deficiencies, anemias, blood dyscrasias, and allied diseases.

Throughout this section there are excellent photographs and colored illustrations of the deficiency states. Also included is a pertinent chart summarizing the important information concerning the vitamins.

In the second half of the book, the author takes up the infectious diseases, the rheumatic diseases, and the uses and abuses of the sulfonamides, penicillin, and streptomycin.

Again, as in previous chapters, an analytic survey of symptomatology is made and the role of important bacteriologic investigation discussed.

In view of the importance of chemotherapeutic agents, the author has gone into considerable detail concerning each with reference to their effect on



From McCombs: *Internal Medicine in General Practice*.

The formation of the blood cells and the mechanisms of the development of anemia. Anemia results: (1) when the integrity of the circulatory system is broken (*acute and chronic hemorrhage*); (2) when there is decreased production of blood by the bone marrow, such as occurs when there is a lack of one or more of the red cell-building elements (*deficiency anemias*), when there is invasion of the bone marrow by tumor cells (*myelophthisic anemias*) or when the function of the bone marrow is depressed by toxins (*toxic and aplastic anemias*); and (3) when there is an increase in the normal rate of cell destruction (*hemolytic anemias*).

specific bacteria. In addition, there are several summarizing charts to help one see at a glance the advantages and disadvantages of the drugs' action on individual organisms.

In the final section of the text, the author takes up the chronic rheumatic diseases, endocrine disorders, vascular disturbances of the extremities, and miscellaneous conditions.

While writing this book, Dr. McCombs was thinking constantly of its practical application by the physician, and he has exerted great effort to clarify and simplify subjects which are by nature very complex. In this aim, he has succeeded in providing methods for more accurate diagnosis and better management of those problems with which the physician is confronted in his daily practice.

RECEIVED THIS MONTH

MINOR SURGERY, By Frederick Christopher, B.S., M.D., F.A.C.S., Associate Professor of Surgery at Northwestern University Medical School, Chief Surgeon, Evanston (Illinois) Hospital. Ed. 6. 1,058 pages with 937 illustrations on 595 figures. Philadelphia, W. B. Saunders Company, 1948. Price \$12.00.

A MANUAL OF PHARMACOLOGY, and Its Applications to Therapeutics and Toxicology, by Torald Sollmann, M.D., Professor Emeritus of Pharma-

cology and Materia Medica in the School of Medicine of Western Reserve University, Cleveland. Ed. 7. 1132 pages. Philadelphia, W. B. Saunders Company, 1948. Price \$11.50.

A MANUAL OF CLINICAL THERAPEUTICS, A Guide for Students and Practitioners, by Windsor C. Cutting, M.D., Professor of Therapeutics, Stanford University School of Medicine, San Francisco. Ed. 2. 712 pages with 30 illustrations. Philadelphia, W. B. Saunders Company, 1948. Price \$5.00.

MEN OF MEDICINE

FOR SERVICE TO THE COMMUNITY

STOCKILY built and six feet tall, with a friendly, weatherbeaten and round, red face, Dr. Archer Chester Sudan likes the rugged life of the out of doors. With an easy-going, cheerful manner, he likes all kinds of people, and likes to help them when they are in trouble. These are some of the reasons why practically overnight he left an enviable teaching and research position at the University of Chicago to spend twenty years in rural Colorado as a general practitioner.

This choice and the devotion he gave to the treatment of the ills of the rural small town people under his care have earned him the first General Practitioner Award of the American Medical Association. Dr. Sudan was selected for the association's newly created gold medal from among hundreds of practitioners whose names were submitted for consideration. The medal was officially presented to him at a special ceremony in his honor during the interim session of the association at Cleveland, January 7. The presentation was made by Oscar Ewing, director of the Federal Security Agency.

This award, similar to the American Medical Association's Distinguished Service Medal, which has been given annually since 1938 for scientific advancement in the field of medicine, is designed

especially to honor a general practitioner who has served as a family physician and who, in that capacity, has received the recognition of his community. The award is known as "the medal of the American Medical Association for exceptional service by a general practitioner."

The award includes not only a medal, but a certificate indicating the reasons for the award.

Among the careers of all the practitioners whose names were submitted for the award, none could compare with that of Dr. Sudan. He had overcome obstacles and endured hardships that would have discouraged and wrecked anyone less vital and cheerful.

In accepting the award, Dr. Sudan said:

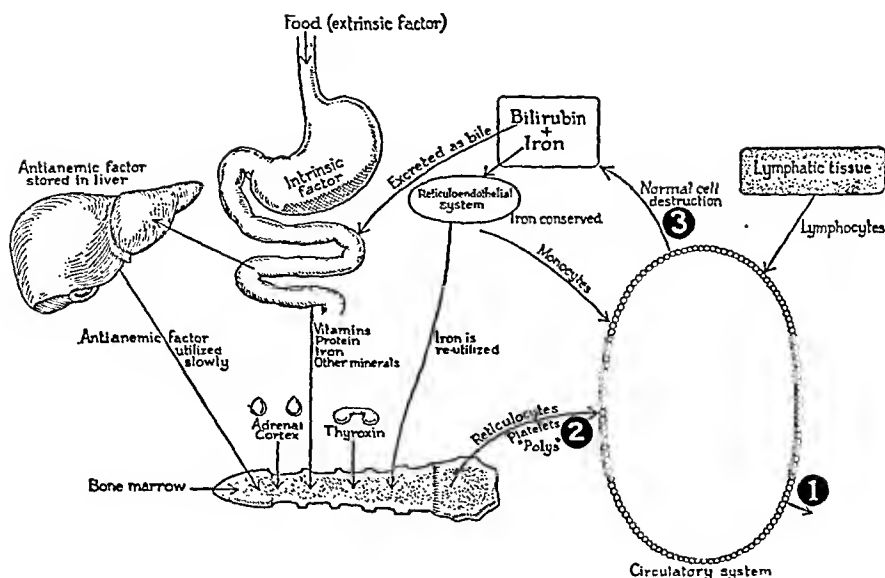
"The good will doctors enjoy today is the

heritage of past generations of general practitioners.

"Therefore, I accept this award as your recognition of thousands of general practitioners. It is a great honor, indeed, to have been selected from among hundreds of equally meritorious candidates to receive this, the first such award. Words cannot express my gratitude.

"General practitioners, today as in the past, are doing their utmost to maintain and enhance their service to the public. They believe, and I believe, that the average American deserves a better-than-





From McCombs: *Internal Medicine in General Practice*.

The formation of the blood cells and the mechanisms of the development of anemia. Anemia results: (1) when the integrity of the circulatory system is broken (*acute and chronic hemorrhage*); (2) when there is decreased production of blood by the bone marrow, such as occurs when there is a lack of one or more of the red cell-building elements (*deficiency anemias*), when there is invasion of the bone marrow by tumor cells (*myelophthibic anemias*) or when the function of the bone marrow is depressed by toxins (*toxic and aplastic anemias*); and (3) when there is an increase in the normal rate of cell destruction (*hemolytic anemias*).

specific bacteria. In addition, there are several summarizing charts to help one see at a glance the advantages and disadvantages of the drugs' action on individual organisms.

In the final section of the text, the author takes up the chronic rheumatic diseases, endocrine disorders, vascular disturbances of the extremities, and miscellaneous conditions.

While writing this book, Dr. McCombs was thinking constantly of its practical application by the physician, and he has exerted great effort to clarify and simplify subjects which are by nature very complex. In this aim, he has succeeded in providing methods for more accurate diagnosis and better management of those problems with which the physician is confronted in his daily practice.

RECEIVED THIS MONTH

MINOR SURGERY, By Frederick Christopher, B.S., M.D., F.A.C.S., Associate Professor of Surgery at Northwestern University Medical School, Chief Surgeon, Evanston (Illinois) Hospital. Ed. 6. 1,058 pages with 937 illustrations on 595 figures. Philadelphia, W. B. Saunders Company, 1948. Price \$12.00.

A MANUAL OF PHARMACOLOGY, and Its Applications to Therapeutics and Toxicology, by Torald Sollmann, M.D., Professor Emeritus of Pharma-

cology and Materia Medica in the School of Medicine of Western Reserve University, Cleveland. Ed. 7. 1132 pages. Philadelphia, W. B. Saunders Company, 1948. Price \$11.50.

A MANUAL OF CLINICAL THERAPEUTICS, A Guide for Students and Practitioners, by Windsor C. Cutting, M.D., Professor of Therapeutics, Stanford University School of Medicine, San Francisco. Ed. 2. 712 pages with 30 illustrations. Philadelphia, W. B. Saunders Company, 1948. Price \$5.00.



ARCHER
CHESTER SUDAN,
M.D.

lem. Often Dr. Sudan's car would get stuck in a snow drift or skid off the road. Frequently he would have to shovel out a pathway for his car through the snow or tear out a post from the roadside and hoist it back on the road.

U. S. Highway No. 40 was kept clear most of the winter, but the side roads very often were impassable. On those occasions ranchers would take him across the country on their bobsleds. Each rancher would transport him across his own land to an adjoining neighbor, where the neighbor would meet him and take him in the same fashion to the next rancher. Although most of the patients lived

in a radius of eight or ten miles from Kremmling, Dr. Sudan, with roadways blocked, often had to travel long circuitous routes to get to them. Some trips took two to four hours each way. Sometimes a patient in need of hospital care had to be brought back to Kremmling and shipped on the highway or railroad to Denver.

Dr. Sudan would carry adequate equipment with him. His binoculars he packed in thermos bottles to keep them from freezing during severely cold weather. He had to do a considerable amount of improvising for usable equipment. He had a shop and laboratory at his home, and could work



OSCAR R. EWING
(left) and
DR. A. C. SUDAN

with his hands fairly well. If, when he arrived at the home of a patient and a bedside table was needed, he would build one on the spot out of packing boxes. If a bedpan was needed he would make it out of the most likely kitchen utensil. An inhaler for a croupy baby he would construct out of a coffee pot or a bucket.

In the crude settings of villagers' and ranchers' homes he performed many difficult surgical operations. During his twenty-one years at Kremmling he has delivered a total of 1,000 babies, 700 of them in the home.

His fees were around \$2 and \$3—the latter figure frequently collected for a complete physical examination. When the patient had no money Dr. Sudan would receive potatoes, eggs, butter, and beefsteaks.

It was not long after his arrival that he became a leader in the community. His philosophical counsel was widely known throughout Colorado's "Western Slope." He gave advice freely—whether a young daughter should marry or finish school first, or whether a rancher should buy an adjoining tract of land, sell his stock at the present mar-

ket, or hold for higher prices. He would attend as many of the public gatherings as he could, take part in the discussions and enjoy the fun of dances and jamborees.

The ranchers in the area are individualists. They do not want too much aid from the government and like to rely on their own resources. Even in the more outlying areas, according to Dr. Sudan, the people expect good medical care. They hear about the miracles of medicine performed in the big city hospitals and expect the country doctor to do as well. So under his guidance and leadership they built a twelve-bed hospital at Kremmling. They recognized readily that the hospital was their responsibility and took an active part running it. It was not too hard to raise money for it. At the Sunday night social gatherings in various parts of the county, where Dr. Sudan was always a welcome guest, the people would dig down in their jeans and hand the money over.

There was, in fact, stiff competition among the donors. If the people of Willowfork raised \$35 or \$40 at one of their gatherings, the people of nearby Troublesome would soon hear about it. They saw

to it that Willowfork would not get ahead of them, and the next social gathering at Troublesome would put \$175 in the collection plate.

The hospital was a boon to the general practitioner, and Dr. Sudan believes that even in such rugged country as the Kremmling area a young doctor could be happy in general practice if he had such facilities. He believes that the enthusiastic youngster, graduating from his internship, wants, probably more than anything else, facilities that will permit him to apply his training. As more hospitals such as the one in Kremmling are established, more doctors will want to practice in rural communities. He recommends that more medical schools place greater emphasis on the preparation of their students for experience such as they face if they select rural areas for their practice.

Not only did Dr. Sudan's reputation as a physician spread throughout the state among men of his profession but he soon established a reputation for his ability to organize and direct community affairs. In 1946 the Colorado State Medical Society named him president of their organization. This was the first time in the society's 77-year history that a physician from a completely rural area had been selected for that office. When Dr. Sudan was

inaugurated for that office during the state meeting in Estes Park, Dr. Dragstedt was present in the audience. He expressed the opinion that when the Colorado physician chose rural practice as a career, research was definitely the loser.

Dr. Sudan has gone much further than providing treatment and care to patients of the area. He was always conscious of the importance of preventive medicine. During his years of rural practice he educated people for better health. His work has been significant in the progress of health education in the state. He was also interested in general education as well, and for many years was a member of the school board in Kremmling.

As a preventive health measure he believes that medical societies should take the lead in improving working conditions and safety programs in agriculture and industry.

Dr. Sudan was nominated for the General Practitioner Award by the Colorado State Medical Society. The nomination was presented to the American Medical Association by Dr. Bradford Murphey, chairman of the state society's board of trustees.

Dr. Sudan is married and has one son, Archer Chester Sudan, Jr., is 19 years old.

LEAD POISONING

ALTHOUGH BAL (British Anti-Lewisite) has been found highly effective in the treatment of acute poisoning caused by toxic quantities of arsenic, antimony, bismuth, and certain other substances, no similar therapeutic effect has yet been reported in cases of lead poisoning. Indeed, one group of investigators found that BAL was actually deleterious in the treatment of lead poisoning. Since plumbism has such a seriously high incidence and severity, further therapeutic trials with BAL have certainly been justified. Telfer, of the United States Public Health Service, has had encouraging results.

BAL combines with arsenic, pulls it out of the tissues, and holds it in combination during excretion, so that the arsenic cannot produce toxic effects while in circulation. Investigators have hoped that BAL would perform a similar function in the treatment of lead poisoning.

Telfer's study embraces only one case; however, this patient had a definite history of exposure, as well as typical symptoms. After the administration of the BAL, the concentration of lead in the urine rose to levels which indicated a toxic dose. Heavier excretion of lead occurred during the second course of BAL. The patient responded well to treatment, was discharged in good health, although the "lead line" persisted in his gums. The author concludes that BAL might well have a place in the treatment of lead poisoning and suggests further study.

EDITORIALS

THE TRAINING AND QUALIFICATION OF AN INTERNIST

SOMEONE, half seriously and half jokingly, has said that an internist was just a family physician with a reputation. As a matter of fact, that is a fair statement of the situation prior to the advent of the "specialty boards."

In most instances those men of broad medical interests who developed skill in diagnosis in obscure cases of internal disorders and achieved a reputation as consultants, thereby became our first internists. Their skill was not a matter of divination; it was based upon a very broad and extensive general experience, together with an ability to make rapid diagnostic correlations of seemingly unrelated phenomena. There were men like Sir James Mackenzie and Kussmaul who derived their skill from general practice; others like Osler who had a long experience in the dead house. There were even surgeons like Harvey Cushing who could qualify in this field, apart from the therapeutic procedures they employed in their work.

In recent years this *qualification by reputation*, for expertness, based on broad and long experience, has been replaced by the method of *qualification by examination*, by specialty boards, of which there are fifteen, loosely bound together by an Advisory Board. These boards derive their authority from the recognized national societies in each specialty and the American Medical Association. Each board establishes its own minimum standards for competence in its special field, and rigidly prescribes the type of training which must precede admission to the qualifying examination.

Thus a rigid structure has been set up, which by indirection has placed our educational sys-

tem and the specialists themselves in a strait jacket. Vigorous protests are heard from the educators on one hand, and clamorous outcries from would-be specialists on the other, when they find difficulty in fitting themselves into these rigid patterns. Add to this the fact that the most successful candidate in an examination is likely to be the man most recently come from academic halls and the wards of our teaching hospitals, and who, therefore, has a great advantage over the man of long experience who may have acquired a vast reputation as a consultant among his fellows in practice. Furthermore it should be recognized that no written examination is likely to reveal that quick, penetrating, almost intuitive insight which enables the master diagnostician to appreciate the subtle interrelationships by which a diagnosis is reached in obscure and puzzling cases.

In this situation one is reminded of the words of Clifford Allbutt, written in 1905:

"It will not be supposed that I ignore the limits and diversities of human faculty, for to one may be given manual dexterity, to another sagacity of observation and inference; nor forget the field of Medicine is so vast that for the narrowness of man's capacity it must be divided: what I urge is that the limits be by personal choice on natural lines, not by the survival of medieval rules, even in their own day vicious, whereby we have made an idol of this divergence, telling each physician, each surgeon, that he shall not follow the bent and growth of his own faculties and the intimate tracks of nature, but that, whatever his capacities and occasions, thus far he shall go and no farther; in the use of his natural gifts he shall be fettered by an artificial rule. Every wise man learns, but too soon, his own defects, his own limits, his own bents, and the natural economy

they impose upon him; but to maintain separate Colleges to intensify schism, to separate the man who treats a disease with one remedy from the man who treats the same disease with another remedy, to distribute half a malady to one practitioner, to another the remnant . . . is contrary to nature, art, and common sense."

In the face of the existing situation in American Medicine, in which we see such rapid and progressive differential specialization, the immediate and crying need is for integration. In making this integration the internist must take the leading role. Integration is his special function, and he must understand that the sick person is more than the sum of his anatomic parts, that he is an individual organism whose ill-being is the expression of its struggle to adapt itself to environmental stresses, internal or external, physical, psychologic, economic, or social. Such a man must synchronize and harmonize the efforts of his specialized brethren much as the conductor of an orchestra does in producing a symphony.

Just as a great conductor may or may not be a solo artist, may or may not be a great composer, so the great internist may or may not have special skills, may or may not have made original discoveries; each of these integrators must have an artist's appreciation of the relations of the parts to the whole. Is it not time that we inquire into the present regimen of training prescribed for internists with a view to determining its success in this direction?

W. S. McC.

MID-YEAR A.M.A. MEETING

THE first midwinter session of the American Medical Association closed in Cleveland, January 8, as a qualified success. The meeting was projected only last June, and the intervening months were apparently too few in which to promote the interest and attendance of general practitioners which was originally contemplated.

In spite of what was to all but official sources a disappointing attendance, the meeting had many excellent features. The first two days were occupied by sessions of the Eighth Annual Congress on Industrial Health. Good papers were presented at these meetings but the majority were scarcely suitable for the greater proportion of the general practitioners for whom the session was planned.

During the first two days when the House of Delegates was also in session, attendance at the Scientific and Commercial Exhibits was poor. This was unfortunate because most of the scientific exhibits were of high caliber and the commercial exhibitors felt badly let down. On Wednesday and Thursday, however, when the regular scientific meetings started, the situation was quite different.

The two days of scientific sessions contained symposiums, panel discussions, and individual lectures. These were, with few exceptions, calculated to give general practitioners information most wanted concerning the everyday problems of practice. Since a future midwinter session has been announced for December of 1948 in St. Louis, an expansion of this type of presentation would be helpful, especially the first two days.

Other features of interest were the Cancer Detection Center operated in the scientific exhibit, and the Clinical Demonstrations and Conference in Dermatology, Diabetes, and Conservation of Hearing. These were operated with skill and presented worthwhile information.

The scientific exhibits were smaller in number than is customary at an Annual Session of the A.M.A. Some of them had been shown before at other meetings, but several were new. Awards were not given for the exhibits. On the whole, those which were designed primarily for general practitioners seemed more appropriately adapted to the purposes of the meeting.

All in all, this first Interim Session conducted an interesting experiment. Whether it will be continued beyond next December's session presumably depends on the attendance at that meeting and the desires of all concerned.

TALCUM POWDER GRANULOMA

TALC GRANULOMA is a serious and not infrequent postoperative complication. It is of more than just academic interest. Numerous authors have recognized the dangers incident to using talcum powder in surgical gloves. The seriousness of the procedure was emphasized a few years ago by Weed and Groves, who made a study of surgical gloves following operative use. These investigators found that in 74.4 per cent of all operations at least one of the gloves used by the operating team had been torn. Over 22 per cent of all gloves examined had been perforated during operation. Obviously, therefore, simple washing of the gloved hand does not suffice to insure against contamination of the operative field.

Following Antopol's report in 1933, several investigators took the view that talc was responsible for various chronic inflammatory lesions which arose postoperatively, and which resembled lesions associated with foreign bodies. Recently, Eiseman and his associates have made a thorough study of patients suffering from chronic lesions attributed to talcum powder. To rule out any other etiologic agents, these inves-

tigators insisted that the pathologic material examined must contain typical talc crystals, around which a foreign body reaction occurred. The granuloma must have occurred at the site of a previous operation, and no other possible source of inflammation could be invoked. Their series contained 37 patients in all of whom these several criteria were fulfilled.

The clinical syndromes were diverse. Most commonly, the patient presented a postoperative wound that had failed to heal (62 per cent). Eighteen patients had chronic sinuses, 5 had fecal fistulas, 7 had intestinal obstructions, and there were various other serious clinical complaints. Tuberculosis was the condition most often confused with talc granuloma. Symptoms had been present for from a few months to twenty-one years. There were 2 deaths in the series of 37 cases.

An adequate substitute for talcum powder has not yet been found. Formaldehyde-treated starch and potassium bitartrate have been used, but these substances have draw-backs. Eiseman and associates suggest, however, that until a better material is found potassium bitartrate, properly sterilized, should be employed.

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This Month in Medicine

ZERO HOUR IN TRAUMA

SPEIDEL of Seattle believes that there is a physical law of repair in the healing of all wounds. Physical, mechanical, chemical, and bacterial changes occur in rapid succession after tissue has been broken or destroyed. Immediate repair aborts many of these changes, and leads to better prognosis and end results. Speidel states the physical law of repair thus: "The healing of a wound is directly proportional to the timeliness of its aseptic coaptation."

Soon after wounding, tissue may be repaired merely by simple, mechanical coaptation. Primary union then occurs, and there is early restoration of function. Within six hours, however, important changes are wrought. The zero hour has passed. healing of the wound becomes more difficult and drawn-out: The earlier the wound is cleansed and the anatomic structures repaired and replaced, the better the chances for quick recovery.

SUGGESTED READING

SPEIDEL, W. C.: The zero hour in the treatment of trauma. *Ann. J. Surg.* 74:576 (November) 1947.

LYMPHOGRANULOMA VENEREUM AND PSITTACOSIS

THE disease agent that produces lymphogranuloma venereum is antigenically related to the agents of psittacosis and meningopneumonitis. Until recently, however, this relationship was observable only by complement fixation test. Some months ago Morgan demonstrated that certain of these antigenic relationships could also be observed by skin-sensitivity tests in animals.

Quite recently Pollard and Witka have found that in human beings a skin sensitizing relationship exists between the agents of lymphogranuloma

venereum and psittacosis. The antigenic kinship of the two agents was shown by inoculating patients suffering from LGV with antigens prepared from cases of psittacosis. Responses were severe and relatively specific. Although these results are interesting in that they extend our knowledge of the relationships that exist between two entirely separate clinical entities, they do not as yet offer a practical method of differentiating the two diseases.

SUGGESTED READING

MORGAN, H. R.: Use of yolk sac antigens for skin tests in rabbits infected with the virus of meningopneumonitis. *J. Immunol.* 54:1 (September) 1946.

POLLARD, M., and WITKA, T. M.: The antigenic relationship of lymphogranuloma venereum and psittacosis by skin test in humans. *Texas Rpt. on Biol. & Med.* 5:288 (Fall) 1947.

STREPTOMYCIN IN TUBERCULOSIS

TAKING cognizance of the developing body of opinion regarding the value of streptomycin in pulmonary tuberculosis, the National Health and Medical Research Council of Australia recently has suggested that the antibiotic be employed in certain conditions of tuberculous infection.

Immediate and dramatic effects may be expected in the treatment of generalized hematogenous tuberculosis and tuberculous meningitis with streptomycin. Final results of treatment, however, are not satisfactory.

Casapneumonic and predominantly exudative forms of tuberculosis respond favorably. The drug is quite effective in controlling an acute spreading lesion following hemoptysis. Improvement usually follows the use of the antibiotic in ulcerative lesions of the larynx, trachea, and bronchus. Preoperative and postoperative use of streptomycin lessens the risk of tuberculous complications and hastens recovery. In genitourinary tract infections the drug produces amelioration of symptoms, but is not cura-

tive. Similarly, in tuberculosis of bones and joints, symptoms regress following use of the drug.

In general, streptomycin produces a bacteriostatic, not a bactericidal effect. Hence, it exerts a suppressive rather than a curative influence upon many forms of human tuberculosis.

SUGGESTED READING

EDITORIAL: Streptomycin in pulmonary tuberculosis. *Med. J. Australia* 2:558 (November 1) 1947.

ULCERATIVE COLITIS AND HOG STOMACH

EHRLICH, of Boston, has developed a treatment of idiopathic ulcerative colitis, on what appears to be sound rationale.

Recognizing that proteolytic enzymes exist in the colon and rectum, Ehrlich points out that gastrointestinal hypermotility, regardless of the reason for its existence, causes a greater concentration of these enzymes in the colon. Hence the colonic mucosa is predisposed to autolysis.

The investigator now assumes that the intestinal mucosa contains "an anti-proteolytic substance," whose function it is to protect the mucosa from autolysis by the proteolytic enzymes of the intestinal contents. This anti-proteolytic substance is thought to be deficient, at least in a relative sense, in the descending colon and rectum, when a state of gastrointestinal hypermobility exists. Hence, the balance of proteolytic and anti-proteolytic enzymes is upset, and the victim is exposed to varying degrees of mucosal autolysis.

Obviously, if this rationale of ulcerative colitis is correct, any compound that contains an abundance of the anti-proteolytic substance might have sound curative properties. Dessicated extract of hog stomach apparently contains this substance. Ehrlich administered this preparation to 15 patients; the dosage was 3 to 6 heaping tablespoonfuls (30-60 gm.) per day, in divided doses before meals.

In all cases the mucosa was restored, ulceration, inflammation, and spasm disappeared, and the mucosa returned to normal. Four patients with secondary infections were treated with sulfonamides. Four patients relapsed and required a second round

of treatment. The hog stomach preparation was administered for a few weeks to three months. Ehrlich regards this treatment as the most specific and promising yet presented for cases of ulcerative colitis of idiopathic origin.

SUGGESTED READING

EHRLICH, R.: Pathogenesis and treatment of ulcerative colitis with extract of hog stomach. *Am. J. Digest. Dis.* 14:294 (September) 1947.

PENICILLIN BY INTRA-ORAL DRIP

TWO years ago Royston and Deverell described a method of administering penicillin solution by intra-oral drip, over a protracted period of time. Further experiences with the technic in the treatment of cases of Vincent's angina, acute tonsillitis, and other disorders have justified another report, which appeared recently.

The apparatus is simple and easily arranged. It consists of a standard drip-transfusion set; the needle is replaced by a piece of rubber tubing 8 inches long, which is bent to form a J on a piece of dental wire in the lumen. The short limb of the J lies in the buccogingival sulcus; the long limb is attached along the outside of the cheek with adhesive tape. The delivery tube is similarly attached to the nose and forehead, thence to the bottle suspended above the head of the bed. The patient may sleep comfortably without disturbing the tube. The solution is administered at the rate of one pint per twenty-four hours.

Patients seem to like this method of medication. Results are thought to be as good or better than can be obtained with other technics, for the drug is in constant contact with infected areas. The patients had no trouble sleeping while the drug trickled slowly down the pharynx. The tube could even be left in place during meals, or while drinking. Royston believes the method of considerable value in the treatment of faucial infections caused by the Vincent's organism, and in various other severe throat infections, including the first day or two of severe faucial diphtheria.

SUGGESTED READING

ROYSTON, G. R.: Penicillin by intra-oral drip. *Brit. M. J.* 2:454 (September 20) 1947.

ACNE ROSACEA

ACNE rosacea is a cutaneous disease of obscure origin. Writers have attributed its appearance to a wide variety of causes—alcohol, menopause, obesity, exposure to the elements, pies, and so on.

Tulipan recently has reported results of his treatment of 96 patients presenting this disorder. On the basis of his studies of these patients' histories, as well as their presenting symptoms, this author concluded that they were suffering from severe vitamin B deficiency. Hence, he administered large doses of this complex, with a resultant clinical improvement of symptoms.

Tulipan concludes that B-complex deficiency is the primary cause of this disease, that many of the other "causative" agents mentioned in the literature are possibly contributing causes, but not primary.

SUGGESTED READING

TULIPAN, L.: Acne rosacea; a vitamin B complex deficiency. *Arch. Dermat. & Syph.* 56:589 (November) 1947.

PENICILLIN DOSAGE SCHEDULES

RESULTS of an experimental investigation, recently reported by Lubrod, suggest that constant and prolonged concentrations of penicillin in the blood stream are not essential for persistent antibacterial effect. Although results obtained with mice cannot be directly applied to human beings, the therapeutic principles involved are probably similar in both mice and men.

Lubrod has found that the antistreptococcal effect of aqueous penicillin G outlasts the measurable blood levels by many hours. He suggests that a large initial dose has a considerable advantage over schedules in which the total dose is fractionated into many equal parts. This is because in the multiple dose schedules the mice die before enough drug gets into the system to control the infection.

On the basis of these findings, as well as certain confirmatory clinical data in the literature, Lubrod concludes that for penicillin-susceptible infections, infrequent dosage of penicillin is safe and probably as effective as the multiple dose routines. For example, 0.18 gm. (300,000 units) of penicillin G

may be administered intramuscularly every twelve hours. Or, if the patient's condition indicates more intensive therapy, an initial dose of 0.6 gm. (1,000,000 units) may be given, followed by the same dose eight to twelve hours later, then reduced doses at twelve-hour intervals.

SUGGESTED READING

LUBROD, C. G.: Comparative efficiency of single and multiple dosage regimens of the penicillins. *Bull. Johns Hopkins Hosp.* 81:400 (December) 1947.

BAGASSE DISEASE

BAGASSE is sugar cane from which the sugar has been extracted. It is pressed into various shapes and used in the manufacture of insulating boards, such as "celotex." Persons working with this material sometimes acquire a respiratory disease, characterized by cough, dyspnea, occasional hemoptysis, night sweats, chills, and low intermittent fever. Miliary mottling occurs in both lungs. Recovery usually follows prolonged illness. The cause of bagasse disease is unknown.

Recently, Gerstl and his associates have attempted to determine the pathogenic properties of bagasse fibers and the microbial content of bagasse suspensions. These investigators inoculated intravenously into rabbits suspensions of unheated bagasse, autoclaved bagasse, and formaldehyde-treated bagasse. The unheated suspensions proved fatal to the animals, except when inoculated in small doses. Numerous necrotizing lesions were found in the kidney and liver, in which fungi were demonstrable; bagasse fibers were not found. When the animals were inoculated with autoclaved or formaldehyde-treated bagasse, no evidence of lesions was observed.

The authors conclude that the bagasse itself did not produce the pathologic conditions characteristic of bagasse disease. Rather the symptoms were thought to have been produced by microorganisms, especially the aspergilli, which were present on or in the bagasse. Bagasse itself is thought to be an inert material.

SUGGESTED READING

GERSTL, B., et al.: Pathogenicity of bagasse. *Arch. Path.* 44:343 (October) 1947.

R. W. C.

Consultation Service

This special consultation information service is offered as a regular monthly feature of *Postgraduate Medicine*. Readers are invited to call on this Service for answers to difficult medical problems from members of our Editorial Board best qualified to help. Each question will be answered by mail and those of general interest will be published each month. Address all communications to Consultation Service, *Postgraduate Medicine*, 512 Essex Building, Minneapolis 2, Minnesota.

FALCIPARUM MALARIA

QUESTION: Will you please advise regarding the management of a case of chronic falciparum malaria. The patient apparently contracted the disease an uncertain length of time ago while working with Navy veterans. Symptoms were precipitated by a change of climate from Maryland to a Southern state during a very hot period.

No chills nor fever occurred but the disease was manifested by malaise, anorexia, and extreme fatigability, especially in late afternoon with a slight rise in temperature. Thin blood smears revealed a high infestation percentage with trophozoites and gametocytes. There is no splenomegaly nor evidences of cerebral damage. There is no history of an acute malarial episode. The patient has never left the limits of continental U. S. and has never employed suppressive medication.

Since the infection was discovered in June, he has been given three therapeutic courses of atabrine with little change in either symptoms or the blood smear picture. A course of plasmoquin is contemplated when clinical improvement occurs. What are the possibilities of precipitating a "black-water" fever episode by further intensive therapy?

M.D.—Indiana

ANSWER: There does not appear to be any possibility of precipitating a "black-water" fever episode by further treatment of this patient. The history of this patient is a very unusual one for infection with *Plasmodium falciparum*. This type of malaria is the one which is most readily controlled by therapeutic courses of atabrine and also the one which gives the fewest number of relapses.

The statement that thin blood smear revealed a high percentage of infection with trophozoites and gametocytes and that there was no change in this condition following treatment is not consistent with what is generally understood to be true in cases of this type. For this reason it is suggested that a prop-

erly prepared slide be submitted to an experienced malariologist to determine if this is actually an instance of infection with *Plasmodium falciparum*.

TO THE EDITOR:

In your issue of *Postgraduate Medicine*, Volume 2, Number 5, November 1947, in answer to an inquiry regarding "Treatment of Lues" you make the following statement:

"It might well be that the relapse of results of serologic tests of the blood are due to the fact that the patient's cerebrospinal fluid is positive."

How much penicillin did this patient receive? This certainly is one factor the doctor asking the question should have asked, because the greater the concentration used, the greater the penicillin blood level would be, making quite an enormous difference to compare a daily wax injection of 300,000 penicillin with one of 1,000,000.

"However, this afforded no demonstrable relief." In what way was there no relief? As the author of this question continues, he mentions that after mapharsen and bismuth subsalicylate, the patient had a negative Kolmer and a strongly positive Mazzini, suggesting that he judges cures by these reactions alone.

In answer to the above problem of penicillin therapy in the light of persisting high serologic titers, the following statement (published in the *Journal of the American Medical Association*, Volume 134, Number 18, August 30, 1947: special article on "The Management of Syphilis" by the Veterans Administration, Washington, D. C.) makes the answer to our problem simple: "The rise in titer or the change from negative to positive that often occurs during or soon after completion of penicillin treatment will not be construed as evidence of serologic relapse."

Very truly yours,

GABRIEL F. GRECO, M.D. Ozone Park, N. Y.

New Drugs

Information published in this department has been supplied by the manufacturers of the products described

PNEUMOCOCCUS POLYSACCHARIDES (TYPE-SPECIFIC) SQUIBB

PURPOSE: To aid in reducing the incidence and carrier rate of pneumonia resulting from the types of pneumococci represented in the antigenic mixture; also in controlling epidemics of these types.

DESCRIPTION: An antigenic solution of the capsular polysaccharides of the most common types of pneumococci. Supplied in two combinations of the types of pneumococci to which adults and children, respectively, are believed to be most susceptible. Each combination contains per cc. at least 0.06 mg. of each of the component polysaccharides, made up in sterile aqueous isotonic solution of sodium chloride containing 0.5 per cent phenol.

INDICATIONS FOR USE: Immunization for older persons and for the very young; also, where possible, for those undergoing surgery or recovering from severe illness; for persons subject to repeated attacks of pneumonia, or unable to tolerate sulfa drugs or other known remedies for pneumonia; in institutions where pneumonia frequently occurs in epidemic form; and for special occupational groups, in whom the incidence of and mortality from pneumonia is unusually high.

ADMINISTRATION AND DOSAGE: For adults and children over 12 years of age, a single 1 cc. injection subcutaneously; for children under that age, 0.5 cc. Immunity usually develops within two weeks and is effective for at least one year. Reactions generally are mild and consist chiefly of slight soreness of the arm lasting for a few days only.

HOW SUPPLIED: Combinations A (primarily for adults) and B (for children) of Solution Pneumococcus Polysaccharides in 1 cc. rubber-stoppered vials, in boxes of 5; and in 5 cc. rubber-stoppered vials, in boxes of 10. Potency period is one year.

PRODUCER: E. R. Squibb & Sons, New York, N. Y.

PYRIBENZAMINE OINTMENT AND CREAM

PURPOSE: Topically applied Pyribenzamine exercises a local antihistaminic action thereby alleviating pruritus and allergic skin manifestations.

COMPOSITION: Pyribenzamine ointment and cream contain a 2 per cent concentration of the active antihistaminic agent. Prepared respectively in a petrolatum base and a water-washable vehicle.

INDICATIONS FOR USE: In the treatment of atopic dermatitis, pruritus ani, contact dermatitis, neuro dermatitis, lichen planus, and lichen chronicus simplex. Also for the general alleviation of pruritus in non-specific skin disorders.

DOSAGE AND ADMINISTRATION: Topical application. A light dressing should usually be applied following application of the ointment.

CAUTIONS: Significant systemic absorption may occur if ointment or cream are applied to extensive raw areas. In rare instances a contact type of eczematous allergic reaction may occur.

HOW SUPPLIED: Pyribenzamine ointment and cream in jars of 50 gm. and one pound.

PRODUCER: Ciba Pharmaceutical Products, Inc., Summit, N. J.

INFAZYME

PURPOSE: Nutrient tonic including the essential amino acids designed especially for the "sickly" child. Supplies the essential and supplementary factors of the vitamin B complex; hematinic tonic; dietary supplement; aids in increasing appetite, and in intestinal absorption and assimilation.

COMPOSITION: Contents per 15 cc. (approximately three teaspoonfuls):

Protein hydrolysate (45% amino acids)	5.0 gm.
Thiamine hydrochloride (Vitamin B ₁)	3.0 mg.
Riboflavin (Vitamin B ₂)	2.0 mg.
Niacinamide	12.0 mg.
Pyridoxine hydrochloride (Vitamin B ₆)	1.0 mg.
Peptonized iron (N.F.)	135.0 mg.
Liver, B-Complex Fraction	67.5 mg.
Rice Bran Extract	67.5 mg.

(Formula expressed in terms of recommended dosage for children 6 to 12 years of age.)

DESCRIPTION: Features a rich fruity taste that particularly appeals to children.

DOSAGE AND ADMINISTRATION: Children 6 to 12 years of age, 5 cc. (one teaspoonful) three times daily. Children 1 to 6 years of age, 5 cc. twice daily. Infants, 5 cc. daily. May be mixed with milk, water, or juices and taken either before or during meals. For infants, may be mixed with feedings.

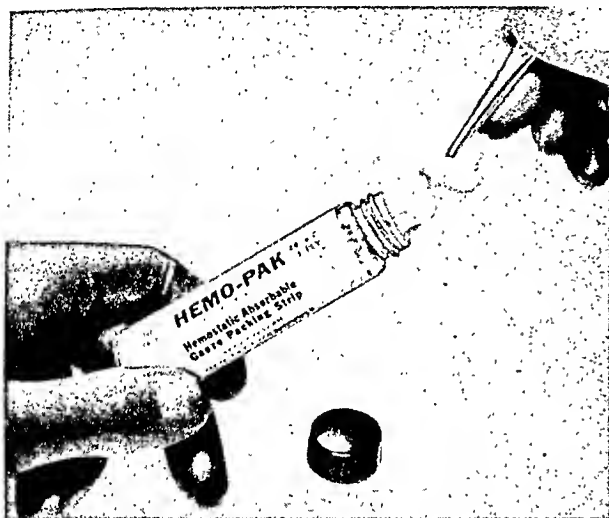
HOW SUPPLIED: 4 oz. and 12 oz. bottles.

PRODUCER: The Wm. S. Merrell Company, Cincinnati, Ohio.

HEMO-PAK

PURPOSE: Hemostatic absorbable gauze and cotton dressings.

DESCRIPTION: Prepared from oxidized cellulose, it effects hemostasis within two minutes after application to the bleeding points. When exposed to blood, Hemo-Pak oxidized gauze or cotton turns black and forms a soft gelatinous mass which readily molds itself to irregular surface contours and controls hemorrhage.



INDICATIONS FOR USE: Hemo-Pak gauze packing strips, 14 inches by 2 inches, are useful in general and urologic surgery for control of venous or capillary hemorrhage or small arterial hemorrhage when suturing or ligation is impractical. Hemo-Pak gauze packing strips, ½ inch by 2½ yards, are especially adapted to otolaryngological procedures. Hemo-Pak cotton pads, 6 inches by 2 inches, are useful in neurologic surgery and ear, nose, and throat procedures.

PRODUCER: Johnson & Johnson, New Brunswick, N. J.

RAYOPAKE

PURPOSE: A new, water-soluble contrast medium for x-ray studies of the uterus, fallopian tubes, bladder, and urethra.

COMPOSITION: A viscous, aqueous solution, containing 50 per cent diethanolamine salt of 2,4-dioxo-3-iodo-6 methyl tetrahydropyridine-N-acetic acid and 4.8 per

cent polyvinyl alcohol, with 0.1 per cent benzalkonium chloride as preservative.

DESCRIPTION: Readily miscible with urine, making aspiration following its use unnecessary. The high viscosity of Rayopake is of particular advantage in outlining the lumen of the uterus, tubes, bladder, and urethra but it prevents its use in other body cavities.

HOW SUPPLIED: Available in 7.5 cc. vials for hysterosalpingography and 35 cc. vials for cystourethrography.

PRODUCER: Hoffman-La Roche Inc., Nutley, N. J.

CREMOMERAZINE AND CREMODIAZINE

PURPOSE: For use in the treatment of pneumonia, meningitis, and other diseases susceptible to treatment by sulfonamides.

COMPOSITION: A new dosage form for sulfamerazine and sulfadiazine.

DESCRIPTION: A palatable, pleasant flavored suspension widely acceptable to the child or adult patient.

INDICATIONS FOR USE: In the treatment of diseases susceptible to sulfonamides.

HOW SUPPLIED: In 16 fluid ounce "Spasaver" bottles.

PRODUCER: Sharp & Dohme, Inc., Philadelphia, Pa.

NITRAMAC TABLETS

PURPOSE: To supply amino acids of a high biologic potency in tablet form, providing a tasteless method of administering oral amino acids.

COMPOSITION: Each tablet contains 0.4 gm. protein. The composition of the protein hydrolysate from which Nitramac Tablets are made is as follows:

Protein	75%
Carbohydrate	14%
Fat	0.3%
Ash	6%

DESCRIPTION: Designed to supplement the dietary intake of protein with protein in predigested amino acid form.

INDICATIONS FOR USE: As a supplement where amino acid therapy is desired in peptic ulcer, pregnancy and lactation, hyperpyrexia, preoperative and postoperative states, digestive deficiencies, extensive burns, diarrhea, and hemorrhage.

DOSAGE: Varied according to needs of the patient. Five tablets four times daily supply 8 gm. of predigested protein.

HOW SUPPLIED: In bottles of 100, 250, and 1,000 tablets.

PRODUCER: The Maltine Company, New York, N. Y.

Medicine Makes News

COMMITTEE ORGANIZED TO ESTABLISH RESEARCH FOUNDATION

IN the first such joint action by the pharmaceutical industry and medical profession, a committee to be known as THE PHARMACEUTICAL-MEDICAL RESEARCH FOUNDATION has been organized to establish a new foundation for basic medical research, to improve the public health. It includes representatives from the pharmaceutical (including the medicinal chemical) industry and the medical profession. The committee will be financially supported, in major part, by the pharmaceutical industry as a contribution to the national welfare.

Representatives from the pharmaceutical industry are: S. DeWitt Clough, chairman of the board, Abbott Laboratories; A. H. Fiske, vice president, Eli Lilly and Company; Elmer H. Bobst, president, William R. Warner & Co., Inc.; John L. Smith, president, Chas. Pfizer & Co., Inc.; S. Barksdale Penick, Jr., president, S. B. Penick & Co.; M. C. Eaton, president, Norwich Pharmacal Co., and Charles Wesley Dunn, of the New York Bar. The representatives from the medical profession are the following officers of the American Medical Association: Dr. R. L. Sencsich, president-elect; Dr. E. L. Henderson, chairman of the Board of Trustees; Dr. Ernest E. Irons, secretary of the Board of Trustees; Dr. Morris Fishbein, editor of the *Journal*, and Dr. Austin Smith, secretary of the Council on Pharmacy and Chemistry. Dr. Sencsich is chairman of the committee.

The foundation will be a wholly public institution in purpose, conduct, and service, including on its governing board distinguished and appropriate representatives of the general public, in addition to

leading representatives of the pharmaceutical industry and medical profession. The board will determine its program of scientific research on the basis of a recommendation by an authoritative scientific advisory committee and the advice of an eminent scientific director. It is contemplated that the initial basic research by the foundation will be in the field of degenerative diseases.

EPILEPSY NOW A REPORTABLE DISEASE

EPILEPSY has been made a reportable disease by action of the Wisconsin State Legislature, in the interest of promoting safety on highways. According to a notice released by the State Board of Health, the Act requires every physician to "report name, age, and address of every person diagnosed as afflicted with epilepsy or similar disorder characterized by lapses of consciousness." It further requires local boards of health or city health commissioners to report to the State Board of Health in writing the name, age, and address of every person reported to them as epileptic, and the State Board of Health in turn is required to make the same report to the motor vehicle department.

In compliance with this same statute, the State Board of Health has promulgated the following definition of epilepsy:

"An affection of the nervous system characterized by attacks of unconsciousness, with or without convulsions, shall be considered as epilepsy in carrying out the provisions of section 146.23, 140.05 (13), and 141.08 of the Wisconsin Statutes."

Correspondence Dept.

TO THE EDITOR:

I have read with interest the article by Dr. Nils Larsen in the November 1947 issue of this journal. His report is of value and contains a rather interesting contribution on the problem of fluorine-containing tablets in the control of dental caries. However, there are a few facts that are obscured by an apparent lack of familiarity with some of the recent work in the dental caries field.

The material discussed in the first part of the paper on nutrition and diet in regard to dental caries has been more or less discarded. Dr. Larsen points out that some candy eaters have no decay whereas many low sugar eaters have considerable decay and suggests that this may be an argument against carbohydrate as a factor in dental caries. We now recognize that there are various degrees of immunity to dental caries and that an individual who is immune to dental caries may eat large quantities of refined carbohydrate without developing caries, whereas the highly susceptible individual may eat only a small amount of carbohydrates and produce much acid in dental plaques. Certain immune individuals may produce the acid in the plaques at such a rate that it does not attack the enamel. This situation is quite comparable to an individual's being immune to a general systemic disease such as tuberculosis, diphtheria, or any of the other communicable diseases, although a different mechanism appears to be involved in the local bacterial enzyme system. The fact that Dr. Howe fed sugar balls to monkeys for eight months and they did not develop dental caries simply re-emphasizes a well known fact that monkeys are relatively immune to dental caries.

On page 363, Dr. Larsen stated, "because of inconclusive evidence, some of the dentists are now using a 2 per cent sodium fluoride solution to paint the teeth three times a year after a thorough cleansing." The inconclusive evidence that Dr. Larsen mentioned has been replaced by the results of very careful studies in Minnesota, Ohio, and other places by the United States Public Health Service and independent investigators who have now established that the application of a 2 per cent sodium fluoride solution to the teeth

of children, four times within a short period after prophylaxis, reduces dental caries by 40 per cent in population groups. The statement about inconclusive evidence should be discarded because of recent studies.

The fact that fluorine-containing tablets did not control dental caries is a very important finding. The blind test which Dr. Larsen used could well be adopted by other investigators of this problem. It is very difficult to evaluate the results of caries control because of the slow process of the disease. It is sometimes a matter of many months or years before carious lesions become observable. The method that he used bears out this observation. It is more important that the lactobacillus counts did not show any reduction on the fluoride-containing tablets. The lactobacillus counts, while not infallible, are valuable indicators of the activity of dental caries and have a place in all well controlled caries studies. Certainly, Dr. Larsen's study is more complete and better controlled than that used to recommend fluoride-containing tablets.

The present status of fluoride-carries investigations justifies the following statements:

1. Fluorine, occurring naturally, in communal water in concentrations of about 1 p.p.m. results in lower caries experience than in nonfluoride water areas in children born and raised on the waters.

2. Experiments on the effect of artificially fluorinated waters, such as are in progress at Kingston-Newburgh, Evanston, Illinois, Grand Rapids, and other cities, are justified and when the results are available the advisability of general fluorinization can be determined.

3. The application of 2 per cent solution of sodium fluoride to the teeth of children in four treatments after prophylaxis results in a caries reduction of about 40 per cent in population groups. Such treatment has adequate evidence to justify general use.

4. Evidence available today does not justify the use of any fluorine-containing compound for home use or self-administration.

Sincerely yours,

Hamilton B. G. Robinson, D.D.S., *Dean,*
College of Dentistry, Ohio State University.

AFTER HOURS

By FRANK G. SLAUGHTER, M. D.

IT is our painful duty to report that the profession of medicine in its present form is all shot to pieces, flat on its back . . . in short, KAPUT. And all because in our zeal to be scientific and make everybody live to a hundred, we have devised a set of instruments of precision which have now turned upon us, Frankenstein-like, to destroy us.

A man in Jacksonville, Florida, named Rowland, has invented a devilishly ingenious little machine which he calls a PHOTOMICRON. Put a specimen of blood under this innocent little apparatus and it tells you the white and red blood counts and the hemoglobin, in less time than it takes to focus an ordinary microscope. *All with the turn of a switch.* Furthermore, this thing really works. We had a demonstration of it the other day and afterwards staggered, pale and shaking, out of the building and across the street to the nearest bar-room for a couple of quick ones to help regain our equilibrium.

It is only a matter of time now until curvaceous blond laboratory technicians will be replaced by massive black and repulsive machines that do everything from blood sugars to urethral smears and print the result on a ticker tape. *The horror of it all!* No more to drop into the laboratory at the end of a long day and get that pre-dinner lift from the sight of white sharkskin stretched snugly over the entrancing curve of the gluteus, or to relax with a cigarette,

between hormone injections, and enjoy the unparalleled revelations of a starched uniform hemline. The world will truly be a sadder place without these things.



BUT all is not lost. We saw this catastrophe coming many years ago and we've had a group of scientists working in our secret laboratory, getting ready for the new world of the machine in medicine. If it's machines they want, we've got them, *dozens of them*, all ready to go at the drop of a dollar . . . in the slot, of course.

We've been holding back our discoveries because we knew the effect they would have on medical practice and we hesitated to unleash the demon of the machine. But now that the secret is out, we're going ahead full steam with our campaign to save the profession from destruction.

Our first invention, the U-REEN-A, is such a simple gadget that we hesitated even to mention it. Attached to the laboratory sink, it shoots a beam of light through a tube of urine, says, "Hm," and dumps the specimen in the sink, stamping *Negative* on the report slip at the same time. Our SUPER-U-REEN-A, however, is something else and well worth the additional cost. (We feel like a dog for introducing commerce into a high planed scientific discussion like this, but after all we have to eat.) It heats the specimen. determines the albumin by a photoelectric

cell, tests for sugar and specific gravity, and examines it with the automatic microscope, all in one operation, completed while you light a cigarette.

One of our more elaborate instruments, the TONSILLOTTRON, or PHARYNGOTTRON, is especially designed to be placed in restaurants. When the patron opens his mouth for the first bite, the instrument shoots a beam of light into the pharynx, measures both diameters of the tonsils, and the elevation above the floor of the fossa in a fraction of a second. Then the mechanical brain instantly calculates the volume of the tonsils and when it reaches a critical level, the instrument says sharply, *"Those tonsils look terrible; they'll have to come out right away."*

While the patient is gagging over his soup, the instrument hands him an appointment with the surgeon owning the instrument and makes a reservation at the nearest hospital. For a slight extra charge, another model will also collect both hospital insurance and professional fee in advance.

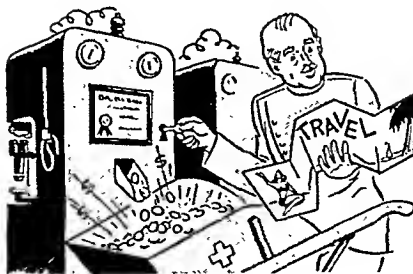


We expect to license our SUPER-LARYNGOTTRON only to certified nose and throat specialists. This model examines the patient who has already had the tonsils removed and murmurs, *"Those tags look pretty bad. Don't you have a lot of trouble with rheumatism, indigestion, insomnia, vague pains, getting up at night,*

belching, gas on the stomach, constipation, impotence, or frigidity?" When the patient answers "Yes," (as who wouldn't) the machine also makes arrangements for the operation and collects fees and hospital insurance in advance.

Because of the high incidence of neurosis and psychosomatic disorders, we have recently invented the HYPNOTRON. An accusing eye stares at the patient while a soft voice intones, "*Sleepy. Sleepy. Sleepy.*" When the head drops and touches a switch, the machine says, "*Now tell me everything.*" As the patient spills the life story, a wire recorder makes a record of it and flashes it by teletype to the editors of "Intimate Romances." At the end the patient is given post-hypnotic suggestions and goosed into wakefulness with an electric shock. An advanced model called the PSYCHOSOMATRON gives electric shock therapy and psychotherapy at the same sitting.

OUR crowning achievement, of course, is the GONOTRON, and our motto is, "*A Gonotron in every man's room.*" This handy little gadget is going to revolutionize venereal disease control. The GONOTRON takes a urethral smear, stains it, and scans it with a cathode ray. When it comes to a pus cell, a smaller ray takes over



and scans the cell. A biscuit-shaped diplococcus hasn't a chance with such an instrument as this. But most important, the GONOTRON doesn't stop at diagnosis; it treats as well. Once it has spotted a gonococcus, it injects 300,000 units of penicillin (Romansky formula, of course) and gives a short recorded sex hygiene lecture.

Modestly, we hesitate to mention such simple devices as our mechanical finger for rectal examinations, or the double model, the GYNOTRON for the gynecologist. We are rather proud, however, of the CORONOTRON. It takes an electrocardiogram, develops it, scans it with the photoelectric eye, and when it reaches a depressed S-T segment, phones the nearest hospital for an ambulance and flashes a *Stand-By* signal to the local undertaker.

We are confident that our machines are going to make a new world for the doctor, the first break he's had since Hippocrates.

With a battery of these mechanical goldmines placed strategically around town, he can sit back and listen to the tinkle of dollars dropping into slots and know that medicine is marching on to new scientific heights and new horizons. In the *Full Life*, doctors will make rounds once or twice daily to empty the tills of these mechanical medicos and stagger to the bank with a load of coin. No more night calls, no more talking to relatives. *What a happy prospect!* Winter at Palm Beach; summer in the Canadian Alps!

And what a change this is going to make in medical education. No more hours spent poring over microscopes, pulling blood smears, or boiling urine. The medical student of tomorrow will work a six hour day, or less, with plenty of time for the real pleasures of the medical course. Then the study of medicine will be what it once was, an occupation for a gentleman.

Well, that's the story. We're off now to collect the take from our experimental battery of machines that we've installed in the local penny arcade, and then off to the races . . .

Damn that telephone! . . . Hello . . . A patient? . . . Female? . . . Give her the Gynotron . . . What? . . . A case of nymphomania . . . Hold everything! We'll treat this case in person!

INTERNATIONAL ASSEMBLY

PUBLIC AUDITORIUM, CLEVELAND, OHIO

NOVEMBER 9 TO 12, 1948

33rd YEAR



Patients rest easier

with Alcohol in Vitadex-B

Alcohol as an analgesic

Patients experience a sense of well-being and confidence—are calm and relaxed—with Alcohol in Vitadex-B. Clinicians report* such satisfactory sedation post-operatively that, in most instances, opiates and other sedatives may be eliminated entirely.

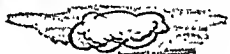
*Behan, R. J., *Am. Jour. Surg.*, 69:227-229, Aug., 1945
Moore, D. C. and Karp, M., *Surg. Gyn. Obst.*, 80:523-525, May, 1945
Craddock, F. H., Jr., *Craddock, F. H., Sr., Mr. of Med. Assoc. of Alabama*, Nov., 1942

Besides the analgesic and caloric advantages of alcohol, this solution supplies the nutritive value of dextrose—plus generous amounts of the B vitamins necessary for alcohol and dextrose metabolism.

SUPPLIED IN CUTTER SAFTIFLASKS

This conveniently combined solution is ready for immediate intravenous administration and comes in 1000 cc. Saftiflasks.

Cutter Laboratories, Berkeley 1, California



Advantages over morphine

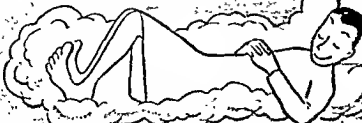
- More prolonged action
- Stimulates respiration
- No nausea or vomiting
- Eliminates any gastro-intestinal disturbances
- Diuretic action
- Produces vaso-dilation without significant change in blood pressure
- No danger of addiction

ALCOHOL IN VITADEX-B CONTAINS:

Thiamine Hydrochloride	5.0 mg.
Nicotinamide	50.0 mg.
Riboflavin	7.5 mg.
Pyridoxine Hydrochloride	3.0 mg.
Dextrose 5%	50 grams

in a choice of

Alcohol 5% in Normal Saline
Alcohol 10% in Normal Saline
Alcohol 5% in Distilled Water
Alcohol 10% in Distilled Water



Experience is the

It's true in medicine

**...William Henry Welch (1850-1934)
proved it in medical history**

Dr. Welch, a renowned American teacher and bacteriologist, discoverer of the bacillus of gas gangrene, knew well the value of experience. He recognized in the study of the history of medicine a means of learning through the experience of others. Eventually, he relinquished his work in pathology to distinguish himself as a teacher of medical history.



best teacher

It's true in cigarettes too!

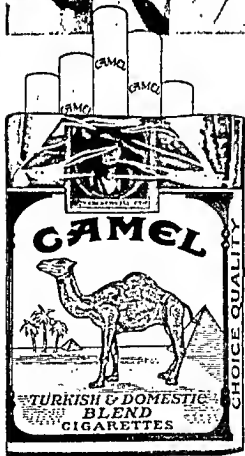
MORE PEOPLE ARE SMOKING CAMELS THAN EVER BEFORE



YES, experience is the best teacher in choosing a cigarette. And with millions of smokers who have tried and compared different brands of cigarettes, Camels are the "choice of experience."

Try Camels yourself. See how the full, rich flavor of Camel's choice, properly aged and blended tobaccos pleases your taste. See if Camel's cool, cool mildness isn't mighty welcome to your throat.

Let your own experience tell you why more people are smoking Camels than ever before.



According to a Nationwide survey:

**MORE DOCTORS
SMOKE CAMELS
THAN ANY OTHER CIGARETTE**

The makers of Camels are understandably proud of the fact that so many, many doctors prefer Camels as the cigarette for their personal enjoyment.

In a nationwide survey by three independent research organizations, 113,597 doctors were asked to name the cigarette they smoked. More doctors named Camel than any other brand.

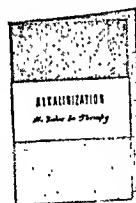
CELESTINS VICHY

Respiratory Infections

When free CO_2 exchange is impaired, respiratory acidosis may supervene. Alkaline fluids are suggested to relieve acidotic distress, and aid in restoring acid-base balance and promoting diuresis.

This agreeable-tasting, refreshing natural mineral water from the famous Celestins spring at Vichy, France, solves the problem of continuing patients on alkaline therapy for prolonged periods.

CELESTINS VICHY is recognized by physicians the world over as a pleasant and effective adjunct in the relief of distress associated with water and mineral imbalance. Have you received this booklet? →



Sole Distributors

BROWNE VINNERS CO., INC.
500 FIFTH AVENUE
New York 18, N. Y.



AN IMPORTANT CONTRIBUTION TO *Peptic Ulcer Therapy*

Mucotin

TRADE MARK

MUCOTIN OFFERS A NEW APPROACH to medical management of peptic ulcer. Its base of highly purified gastric mucin provides a thick, tenacious coating of ulcer and gastric mucosa, resistant to diffusion of pepsin and HCl. It inhibits pepsin activity, while its antacid components, in balanced dosage, neutralize excess acidity. Mucotin is virtually histamine-free, will not produce acid rebound. Mucotin tablets are pleasantly flavored, highly palatable and have a minimal effect on gastro-intestinal function.

Mucotin

EACH MUCOTIN TABLET CONTAINS:

Gastric Mucin 2½ gr. (0.16 gm.)

Dried Aluminum Hydroxide Gel 4 gr. (0.25 gm.)

Magnesium Trisilicate 7 gr. (0.45 gm.)

Dose, 2 tablets every 2 hours, or as directed by physician. For optimal effect, tablets should be well chewed and patient advised not to drink liquids within a half hour after ingestion of tablets.

Supplied in dose dispenser packages of 50 tablets.

Harrower

LABORATORY INC • GLENDALE, CALIFORNIA

Digitaline Nativelle puts out the "cat"



Dosage by "cat units" is eliminated by prescribing Digitaline Nativelle, the chief active principle of digitalis purpurea. Digitaline Nativelle affords simplified dosage and uniform cardiotonic action. . . . is therefore a preparation of choice whenever digitalis therapy is indicated.

Digitaline Nativelle
affords 5 advantages . . .

1. Uniform potency by weight.
2. Identical dosage and effect when given intravenously or by mouth.
3. Virtual freedom from gastric upsets and untoward side effects.
4. Uniform, rapid absorption and action, determinable by the clock.
5. Active principle indorsed by leading cardiologists.

Extraneous substances and their untoward side effects, so common with the use of crude preparations, are virtually eliminated by prescribing Digitaline Nativelle, the chief active principle of digitalis.

RAPID DIGITALIZATION . . . 1.2 mg. in equally divided doses of 0.6 mg. at three-hour intervals.

MAINTENANCE: 0.1 or 0.2 mg. daily depending upon patient's response.

CHANGE-OVER: 0.1 or 0.2 mg. of Digitaline Nativelle may advantageously replace present maintenance dosage of 0.1 gm. or 0.2 gm. of whole leaf.

For faster, uniform action with less "reaction" . . . prescribe Digitaline Nativelle.



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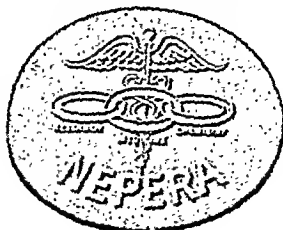
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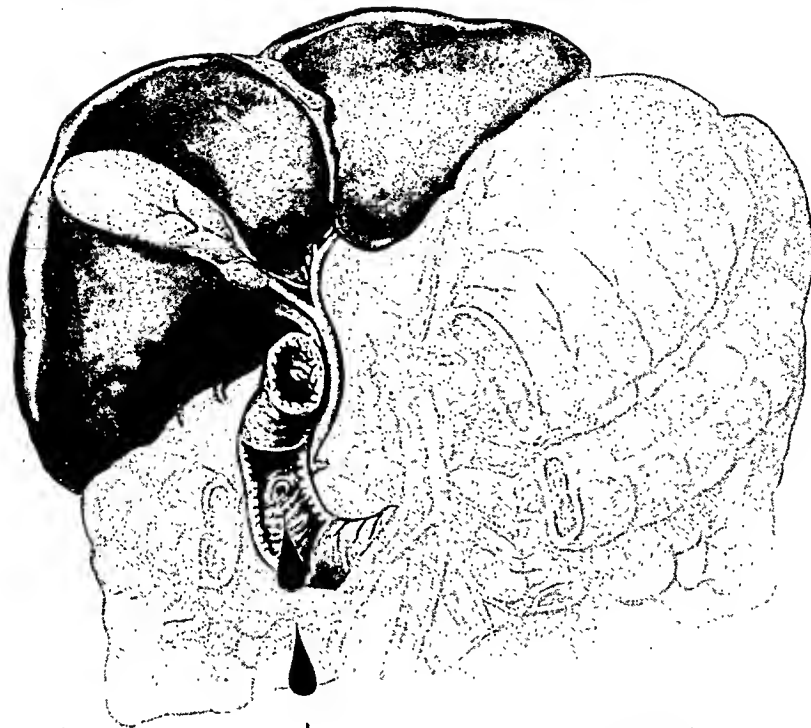
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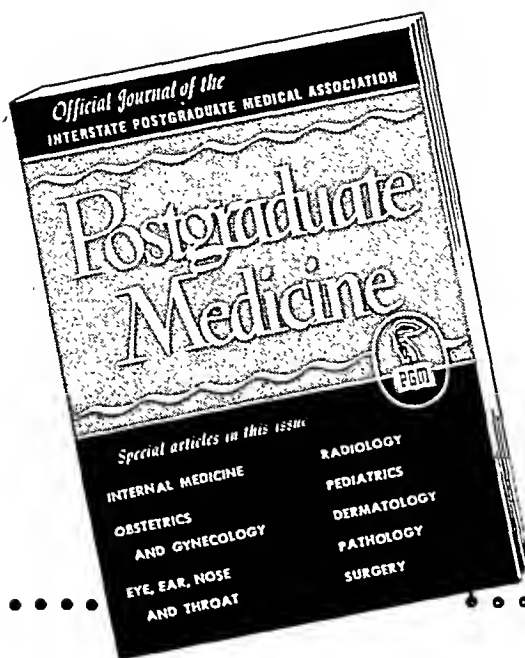


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1. Lehr, D.: Proc. Soc. Exper. Biol. & Med. 64:393, 1917.

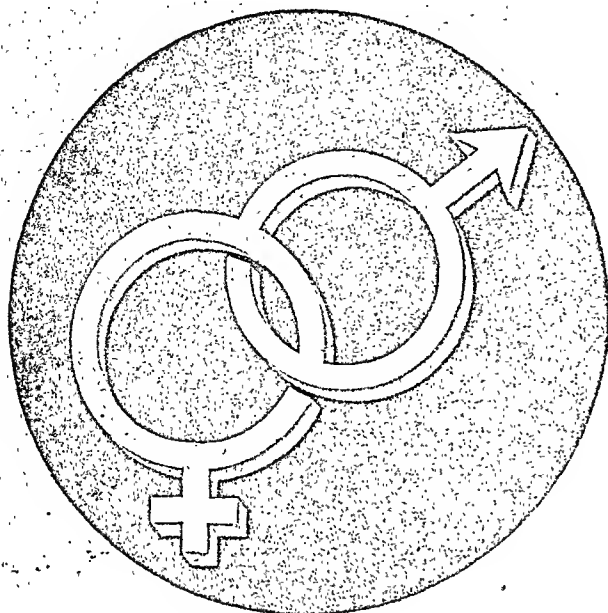
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1. Gusberg, S. B., Am. J. Obst. & Gyn. 50:502, 1945

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Postgraduate Medicine

VOLUME 3, Number 6

JUNE 1948

Special articles in this issue

ADVANCES IN THE TREATMENT OF GLAUCOMA

Edward J. Currah, M. D., UNIVERSITY OF KANSAS
SCHOOL OF MEDICINE, KANSAS CITY, KANSAS

RADIOACTIVE IODINE IN THE STUDY AND TREATMENT OF THYROID DISEASES

F. Raymond Keating, Jr., M.D., DIVISION OF
MEDICINE, MAYO CLINIC, ROCHESTER

PSYCHOSOMATIC GYNECOLOGY

J. P. Pratt, M.D., HENRY FORD HOSPITAL, DETROIT

INDEX TO VOLUME III

Diagnostic Clinics

CARCINOMA OF THE LUNG

Alton Ochsher, M.D., MICHAEL DeBAKEY, M.D.,
AND LEONARD DIXON, M.D., THE TULANE UNIVERSITY
SCHOOL OF MEDICINE, NEW ORLEANS

DIAGNOSIS AND TREATMENT OF THE ANEMIAS

Cyrus C. Sturgis, M.D., UNIVERSITY OF MICHIGAN
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OSTEOPATHIES ENCOUNTERED IN THE ENDOCRINE CLINIC

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See Table of Contents on Page 5

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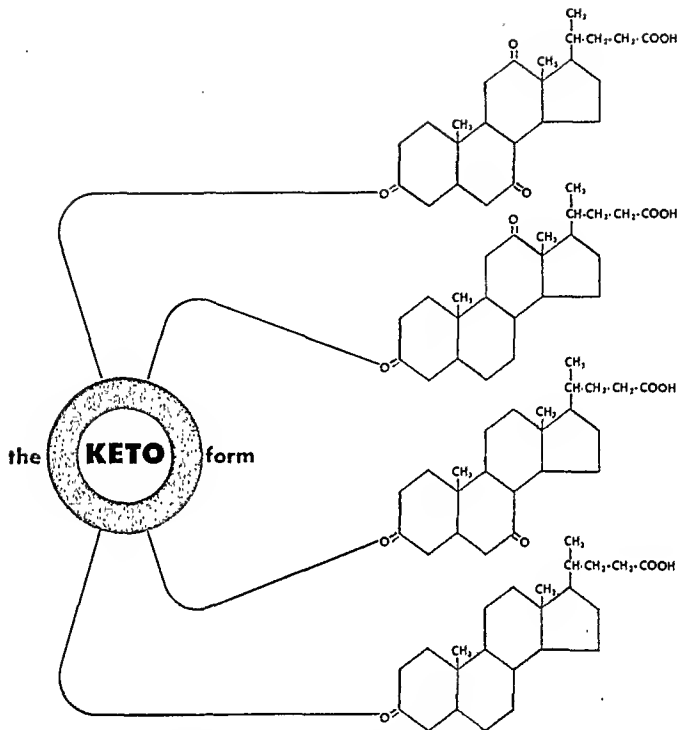
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Table of Contents

VOL. III, No. VI

Special Articles

ADVANCES IN THE TREATMENT OF GLAUCOMA. Edward J. Curran, M.D.	399
RADIOACTIVE IODINE IN THE STUDY AND TREATMENT OF THYROID DISEASES. F. Raymond Keating, Jr., M.D.	410
PSYCHOSOMATIC GYNECOLOGY. J. P. Pratt, M.D.	423

Diagnostic Clinics

CARCINOMA OF THE LUNG. Alton Ochsner, M.D., Michael DeBakey, M.D., and Leonard Dixon, M.D.	427
DIAGNOSIS AND TREATMENT OF THE ANEMIAS. Cyrus C. Sturgis, M.D.	441

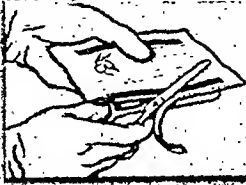
Scientific Exhibit

OSTEOPATHIES ENCOUNTERED IN THE ENDOCRINE CLINIC. Rita S. Finkler, M.D., and George M. Cohn, M.D.	449
--	-----

Departments

THE MEDICAL BOOKMAN. <i>The Foot and Ankle</i>	465
MEN OF MEDICINE. <i>Isaac Arthur Abt, M.D.</i>	468
FOREIGN SURGICAL CONFERENCES. <i>Report of a Trip.</i> Waltman Walters, M.D.	475
EDITORIALS. <i>Vagotomy Versus Gastric Resection • Whither Medical Specialism?</i>	479
THIS MONTH IN MEDICINE. <i>Annual Mass Radiography • Inactivation of Hepatitis Virus • Leprosy • Relaxation in Children • Cytology and Gastric Carcinoma • Antidote to Vitamin D • Tooth Erosion by Fruit Juices • Diphtheria Carriers • Epinephrine Spray</i>	482
CONSULTATION SERVICE. <i>Compressed Air Injury</i>	485
NEW DRUGS	486
LEAVES FROM A DOCTOR'S DIARY	488
INDEX TO VOLUME III	490
AFTER HOURS	494

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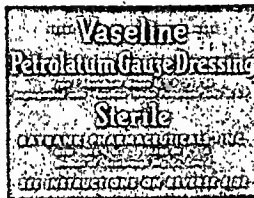
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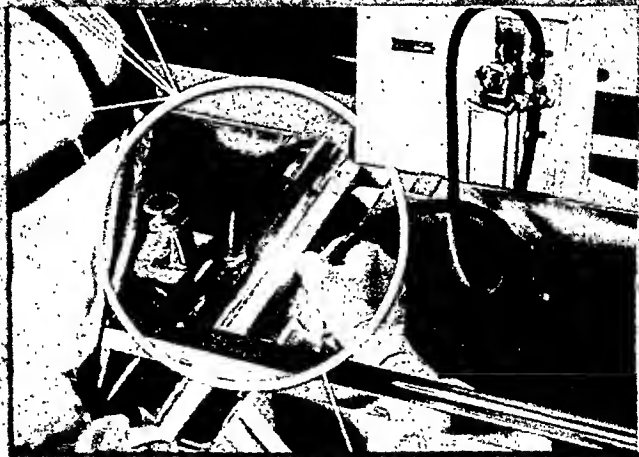
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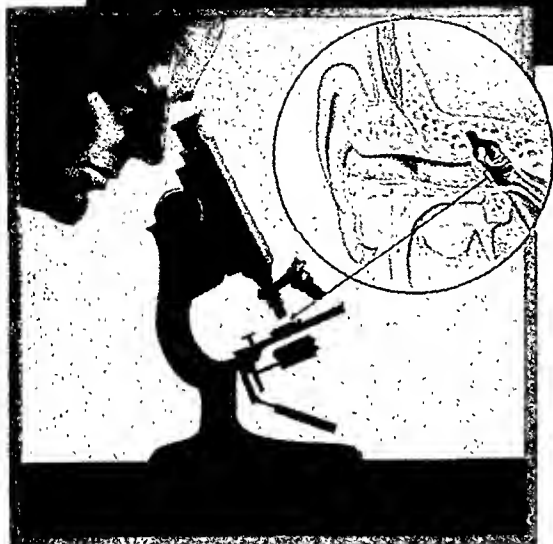
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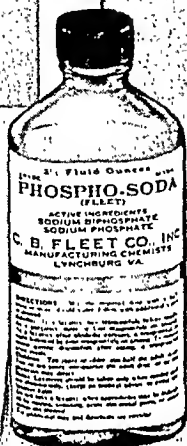
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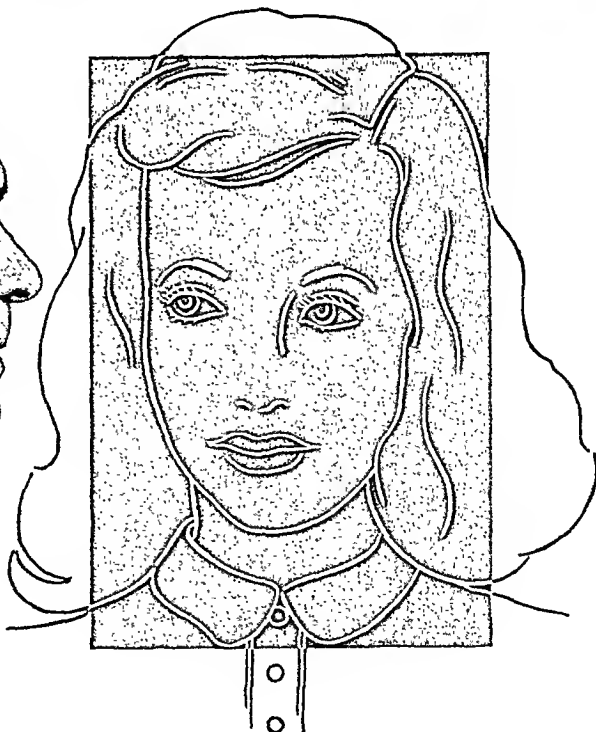
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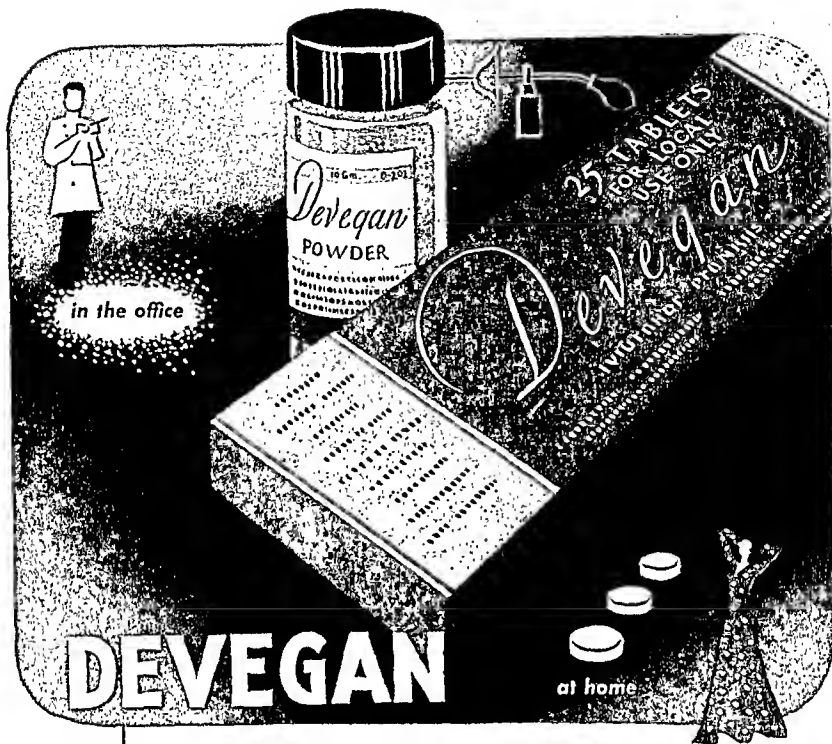
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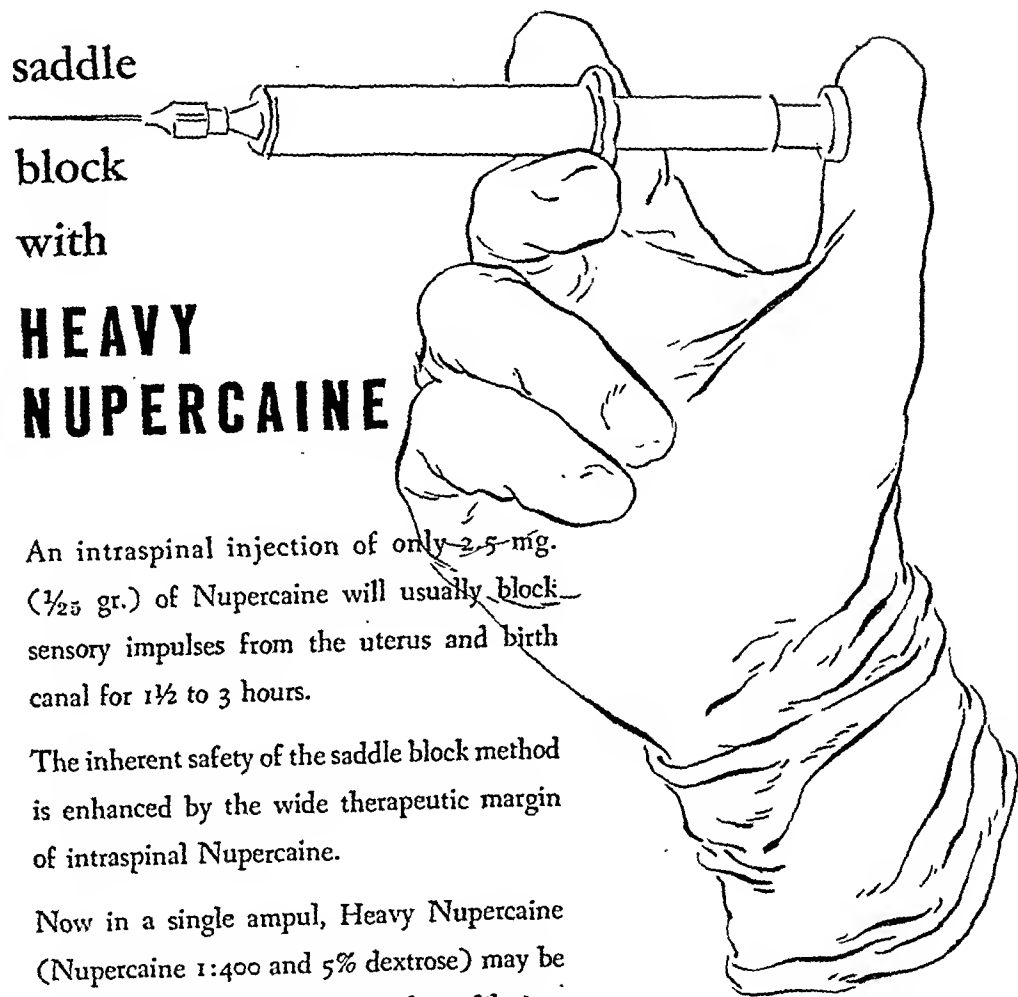
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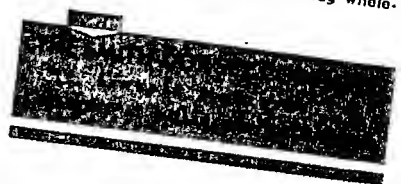
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Advances in the Treatment of Glaucoma

THE JOSEPH SCHNEIDER FOUNDATION EYE PRESENTATION

EDWARD J. CURRAN*

UNIVERSITY OF KANSAS SCHOOL OF MEDICINE, KANSAS CITY, KANSAS

I AM indebted to the Schneider Foundation for the honor of appearing before you tonight. Dr. Schneider was an outstanding eye surgeon of the middlewest, whom I have known and respected for his skill and humanity from the early days of my medical studies. I feel grateful for the opportunity of giving this short address on ophthalmology, a subject which was dear to his heart. His kindly spirit and ever-anxious mind was troubled with the problems of blindness from different causes, and among the greatest of these was blindness from glaucoma.

There are 200,000 blind people in America. It is claimed that 20,000 are blind in both eyes from glaucoma, and a great many more are blind in one eye from the same cause. Of course, these statistics refer to all types of glaucoma. In this address I am confining my remarks to chronic primary glaucoma, the most prolific source of blindness of the various types of glaucoma, and perhaps the least understood. My talk is not concerned with the large number of secondary glaucomas. My chief object is to

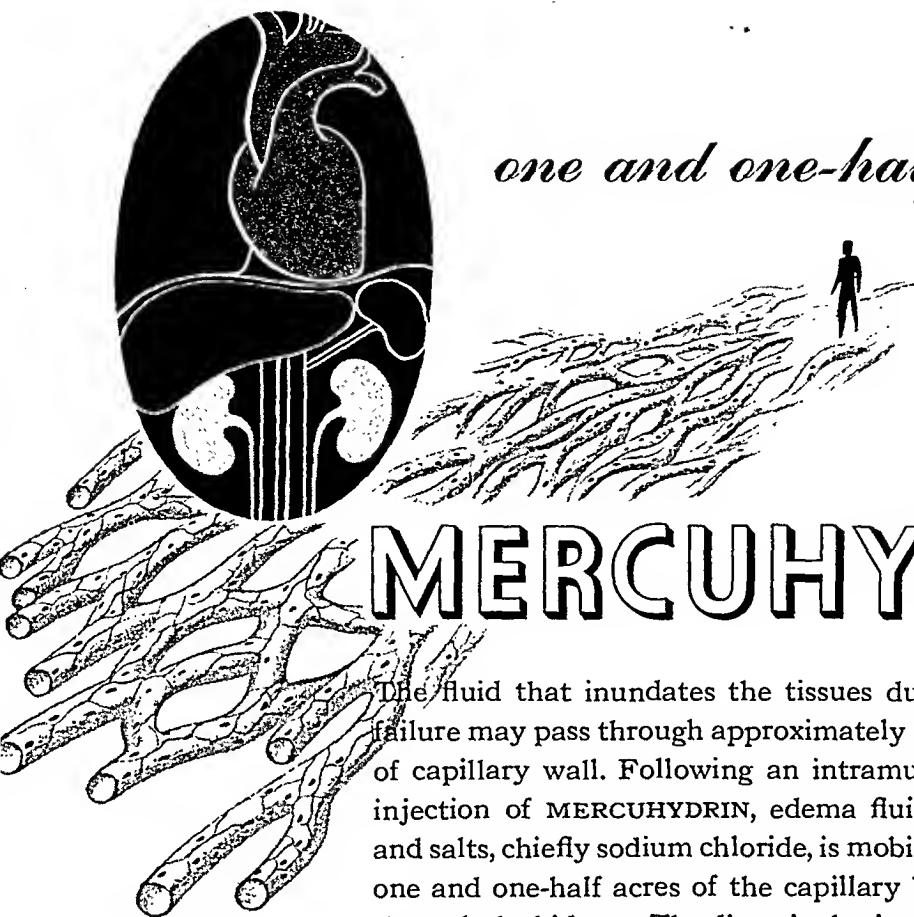
establish the fact that chronic primary glaucoma is not a disease, but simply a congenital defect in the development of the eye which causes it to fail to meet the normal functions in the production of aqueous and the exit of aqueous from the eye. I hold that essentially chronic primary glaucoma is not caused by any toxic condition. It is true that its course may be influenced by such conditions and by psychosomatic effects; but even this does not put it into the class of a disease. (Until we are able to separate congenital defects from secondary disease, we are not on firm ground.)

I wish first to stress the important points in the anatomy of the eyeball which shall be referred to in this address (Figure 1). A rough reminder of the physiologic interchange of fluids is also necessary. Five points should be kept in mind. They are: (1) formation of aqueous in the posterior chamber by the ciliary body; (2) flow of aqueous from the posterior chamber through the pupil into the anterior chamber, thence through the (3) spaces of Fontana, at the so-called filtering angle into the (4) canal of Schlemm, to be carried into the venous circulation by the aqueous veins which connect with the canal of Schlemm, and (5) a possible absorption of aqueous by the iris and the retinal capillaries. The constant, though slow pro-

*Professor of Ophthalmology, University of Kansas School of Medicine, Kansas City, Kansas.

Presented before the meeting of the Interstate Postgraduate Medical Association of North America, St. Louis, Missouri, October 14 to 17, 1947.

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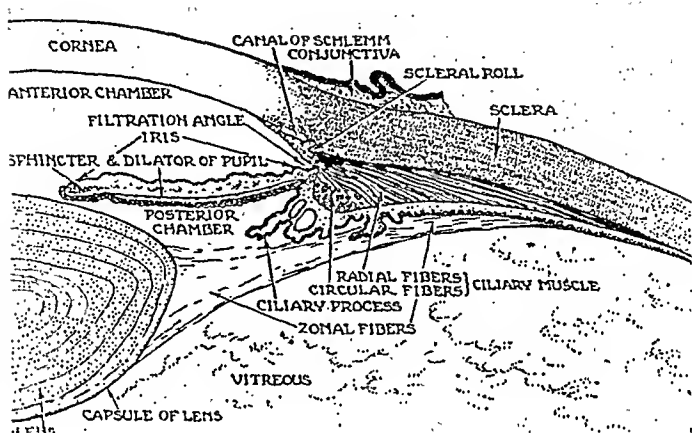


Figure 1. Detail of the anterior segment of the human eye. Redrawn from Maximow and Bloom from Weymouth in *Fulton-Howell Textbook of Anatomy*, published by W. B. Saunders Company.

partly compensated for by the weakness of young growing tissue which causes the eyeball to be enlarged with dire results to the appearance and efficiency of the eye.

THE ophthalmologist comes in contact with this phase of chronic primary glaucoma at the birth of the child, or shortly thereafter. It may be either megalophthalmos anterior, or buphthalmos (an enlargement of the whole eyeball). Whichever it happens to be, it is still prenatal glaucoma, part of our concept of chronic primary glaucoma seen in later life. The pressure may cause a continuous increase in the size of the eyeball; as time goes on, it may be called infantile glaucoma, and later juvenile glaucoma. At this stage the size of the eyeball does not increase, but the pressure begins to do more damage. In adult life it is called chronic primary glaucoma, which is simply a later, delayed stage of some congenital anatomic defect lessening the normal outflow of aqueous from the anterior chamber, complicated with the normal growth or alteration of tissues later in life, without any toxic or inflammatory process except the congestion

caused by the intraocular pressure. This happens in acute exacerbations of chronic primary glaucoma. The intraocular pressure is the cause of such so-called inflammation, more properly called congestion, and not the result of any virus or bacterial invasion, or by allergy. These may contribute to congenital defects just as they do in cases of normal development.

Eyes with congenital defects in the filtration angle may be compensated for by a slight increase in the size of the cornea together with a consequent lengthening of the canal of Schlemm and enlargement of the angle of filtration, but when the lens begins to increase in size in later life, the filtering angle is lessened and leaves less exit for the aqueous, and the pressure inside the eye increases. Again, there are other cases in which the cornea is normal or less than normal in size. The anterior chamber is necessarily shallow and the canal of Schlemm is shorter because of the smaller circumference of the cornea. Any increase of the size of the lens would decrease the exit of fluid from the eye by impeding the flow of aqueous into the anterior chamber through the pupil and by pushing the iris forward, further reducing the filtering angle. In

addition, some of the aqueous might have an easier exit from the posterior chamber into the vitreous chamber, causing edema of the vitreous and pushing the lens forward still farther. Too often a toxic condition has been assumed instead of a mechanical defect in explaining the edema of the vitreous in such cases.

How does glaucoma cause blindness? Certainly by pressure on the retina and the choroid, for here there is both pressure and stretching of these delicate nonmedulated fibers. The stretching at the optic disc is the more disastrous. The lamina cribrosa, through which the optic nerve fibers pass, is really part of the sclera, or perhaps, trabecular projections from the sclera, trying to enclose the contents of the eyeball and yet permit the optic nerve fibers to pass through the brain. However, it is part of the envelope which holds the contents of the eyeball. Being the weakest part, any pressure within the eyeball will press the lamina back, causing a cupping of the disc and in being pushed back, will produce a certain amount of stretching of the optic nerve fibers which come from the ganglia cells of the retina. Remember that inside the eyeball these are delicate non-medulated fibers very susceptible to injury from pressure or stretching. If the lamina cribrosa is weak, it takes less pressure to push it back and produce stretching damage.

It seems to me that the lamina cribrosa is an important part of the structure containing the contents of the eyeball concerned in glaucoma; for we have eyes of normal intraocular pressure, with a weak lamina cribrosa, which are subject to this nerve stretching process, and the retinal cells in such eyes may not suffer greatly from pressure. The greater damage in such cases is done by stretching of the delicate, nonmedulated optic nerve fibers before leaving the eye through the lamina cribrosa. Where there is a strong lamina with high pressure, the retinal cells suffer more from pressure than from stretching of nerve fibers. Some laminae cribrosa are so strong that high pressure does not cause cupping of the disc and consequent stretching of the optic nerve fibers. In such cases the sight may be prolonged with comparatively high

pressure. I have pointed to this fact in previous papers on this subject. Whether the intraocular pressure has damaged the retinal cells or the choroid, or the stretching process is added, the end result is atrophy of the optic nerve and loss of vision, more quickly if the lamina cribrosa is weak. All is due to pressure. It is therefore imperative that the first requisite in all cases of intraocular pressure is to reduce the pressure. If the lamina cribrosa is strong the eyesight will last longer, but if it is weak and easily pressed backward, the pressure should be reduced regardless of how high or low it may be.

How about the cases in which there is progressive cupping of the disc due to a weak lamina cribrosa under normal pressure? The so-called normal pressure should be reduced, for it is not normal, but too high, in relation to the weakness of the lamina cribrosa. I cannot stress too much the relation of the intraocular pressure to the strength of the lamina cribrosa. A weak lamina may be pushed back by a so-called normal pressure; on the other hand, a strong lamina may bear a great deal more pressure for a long time without comparatively rapid blindness. All these things must be carefully considered when contemplating either the medical or surgical treatment of glaucoma.

The treatment of glaucoma by miotics should be attempted before any operative procedure is contemplated. The miotics contract the pupil and tend to stop a clogging of the filtering angle. In other words, they act in a mechanical way to clear the filtering angle and allow easy access of the aqueous to the canal of Schlemm through the spaces of Fontana and thus reduce the pressure. Unfortunately in some late cases they increase the pressure by causing congestion of the intraocular vessels. If we use miotics on the patient's first visit, we should keep the patient under observation for several hours and not dismiss him until a reduction of the pressure becomes evident. A miotic should not be prescribed for a patient with glaucoma without noting its immediate effects on the first

day and its effects under varying conditions for weeks and months following. Of course, in all glaucoma cases visual acuity, intraocular pressure, and fields of vision should be taken. The most important of these is the field of vision. Many patients can be carried for years under miotics, but it must be kept in mind that the progress of the case can be judged principally by any variation in the field of vision, whereas the visual acuity as tested by a chart is sometimes misleading.

What kind of miotics may we use? First, use one which will reduce the pressure. Find the minimum amount necessary to keep the pressure normal and the field of vision intact, and do not use a greater amount. If the patient becomes sensitive to eserine and pilocarpine, change to acetocholine, doryl, or some of the other miotics. The latest miotic seems to be di-isopropyl fluorphosphate (D.F.P.). I have had little experience with this drug, but its chief virtue seems to be that one drop a day or week is all that is necessary for miosis, while many drops each day by older miotics are necessary.

ONE of the greatest difficulties in treatment is that the eye becomes sensitive to any miotic. It may produce a quiet iritis, which is unwelcome, because there may be pigment deposits on the anterior capsule creeping toward the center of the pupil. However, before it does this, it may cause an allergic conjunctivitis. Examine deposits on the anterior capsule of the lens. These pigmentary deposits tend to migrate beyond the edge of the iris to the pupil center and thus diminish the vision. The quiet iritis caused by miotics may also produce posterior synechiae, thus impeding the flow of the aqueous into the anterior chamber with a consequent pushing forward of the iris and narrowing of the filtering angle without producing the typical iris bombe.

There are several new miotics still in their experimental stage. I have not found any to be superior to the older ones, but they may be used when the patient becomes allergic to eserine, pilocarpine, etc. While I advocate the contin-

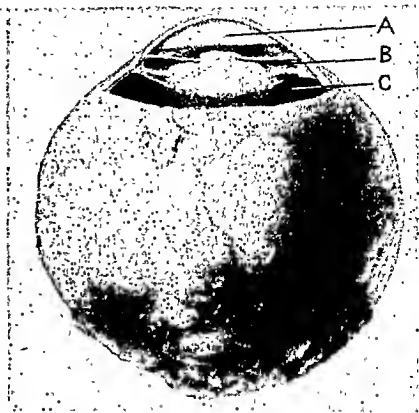


Figure 2. Photograph showing the position of the lens *in situ*. The eye was removed after death. On one side the iris appears to be adherent to the cornea beyond the canal of Schlemm, but there is no history of intraocular pressure. The suspensory ligaments were very faint in the photo and were retouched. The photograph shows the anterior chamber (a), the posterior chamber (b), and the vitreous chamber (c).

uous use of miotics with proper judgment in the local treatment of glaucoma with other general measures, I must stress the importance of frequent examinations and continuous study of the fields of vision. Visual acuity may be normal even with a diminishing field of vision until it reaches the fixation point, or the acuity may be reduced by vitreous opacities or many other causes not due to glaucoma. The visual acuity, without the record of the field of vision, can give no reliable information as to the progress in any case of glaucoma. If there is persistent rise of intraocular pressure there must be a loss in the field of vision.

In glaucoma it is essential to have the field of vision checked continuously. Several larger or smaller targets should be used in the perimeter to determine accurately any change in the field of vision. If there is a failing of sight under miotics and general treatment, and a

diminution of the field of vision exists, operation is indicated. There are several operations which may relieve the condition, each having its place in the operative treatment of glaucoma.

SCLERECTOMY

Draining under the conjunctiva is established by some of the various forms of sclerectomy. The conjunctiva is dissected down from above in the Elliott operation and a hole is trephined into the anterior chamber at the corneal scleral junction, or a fusiform scleral corneal sclerectomy is made at the limbus (LeGrange's operation). There are many modifications of these operations; in fact, I have one which I shall briefly describe. The success of these operations depends greatly on having the sclerectomy hole and subconjunctival tissue bathed in aqueous. If vitreous appears in the sclerectomy hole it means failure. Proliferation of fibrous tissue takes place and the filtration hole closes with a return of the glaucoma; but not so likely if the wound is bathed in aqueous. There is something about aqueous which prevents, or at least does not encourage, proliferation of fibrous tissue while vitreous seems to stimulate it, and thus close the filtration trephine.

SCLERECTOMY usually fails in young people, whether the sclerectomy trephine hole is bathed in aqueous or not. This appears to be due to the vitality of the young tissue which needs but little stimulation to proliferate. In cases of inflammation, sclerectomy is also unsatisfactory at any age whether the sclerocorneal opening into the anterior chamber is bathed in aqueous or not. In every increased vascular congestion, whether passive or active, there is an exudate with colloidal substance which stimulates proliferation of connective tissue to close the filtering hole. This is the experience of anyone who has done a great many operations on glaucomatous eyes.

From these necessarily short remarks on so large and great a subject it will be seen that our great difficulties in doing any form of sclerectomy

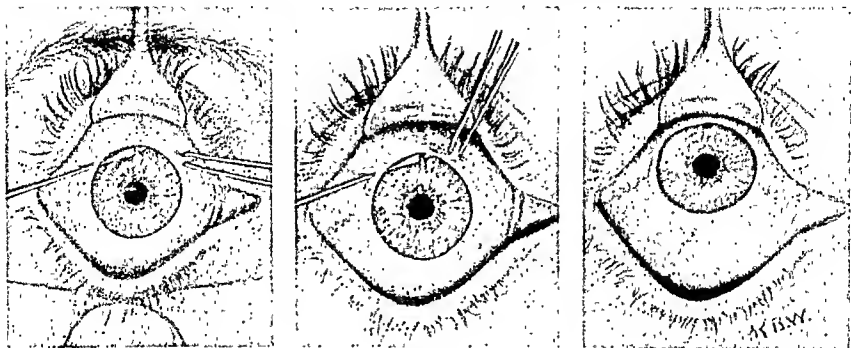
are to be met with in the young, even up to about 40 years of age, or on the inflamed eye of any age, and in cases where vitreous appears in the sclerectomy hole at the time of operation or a little later.

PERIPHERAL IRIDOTOMY

After years of experience with various kinds of operations for the relief of chronic primary glaucoma, I find that there are only two types of glaucoma operations which appeal to me. One is peripheral iridotomy, the drainage (Figures 3, 4, and 5) from the posterior chamber to the anterior through an operative hole in the periphery of the iris, as described by me in 1920. I feel that my twenty-eight years of experience with this procedure have established its benefits and its limitations.

Peripheral iridotomy has been confused by some with Fuch's transfixation operation for iris bombe. It is entirely different, and for a different condition. Moreover, peripheral iridotomy is much better for iris bombe than the transfixation operation. In cases of acute or chronic glaucoma when the iris extensively shows the contour of the lens, there may be no posterior adhesions of the iris to the lens and there may be no (even slight) deposits of iris pigment on the anterior capsule of the lens, and certainly no iris bombe, and a so-called transfixation operation for this condition may be disastrous. Of course, with prolonged use of miotics, posterior synechia may take place; but I have never seen iris bombe from this cause in chronic primary glaucoma.

If the prolonged use of miotics causes posterior synechia, there may be anterior synechiae in the periphery, or at least a lessened exit through the spaces of Fontana leading to the canal of Schlemm. I wish to emphasize that iridotomy must be done in the periphery in any case, even in cases of iris bombe. A hole is cut through the iris about a millimeter or less from its periphery, a position least likely to produce much bleeding unless the ciliary body is invaded. If the ciliary body is punctured, there will be excessive bleeding.



Figures 3, 4, and 5. The procedure in peripheral iridotomy, as described in the text, is illustrated in these photographs.

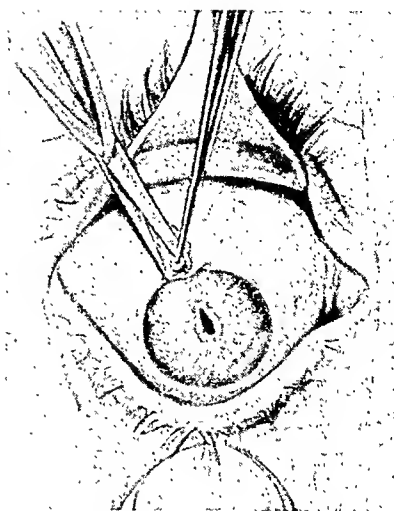
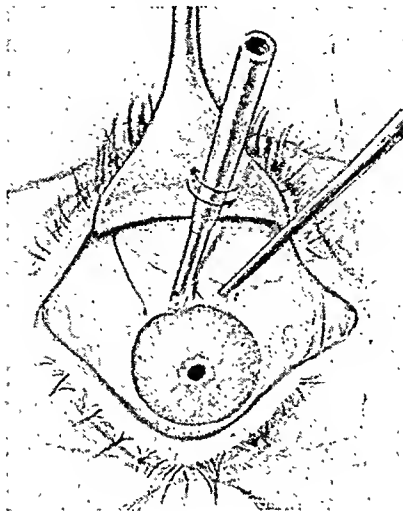
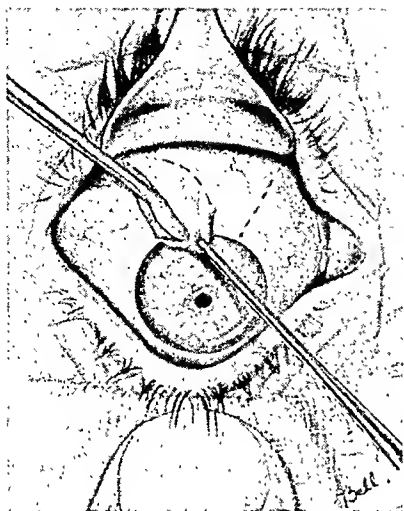
Peripheral iridotomy is done by inserting a Lang, Knapp, or any other fine thin knife, at the corneal scleral junction, passing it into the anterior chamber with the back of the knife toward the pupil, engaging the periphery of the iris and on pushing it forward rucking it up, enabling the puncture and the counter puncture of the iris, still passing the knife forward. In order to make the hole in the periphery of the iris, we should push the knife forward toward the limbus on the other side to cause a counter puncture at the corneal scleral junction. This should be done so that the counter puncture of the corneal scleral junction coincides with the position of the canal of Schlemm so that it would cut through the pectinate ligaments and provide an easy exit of the aqueous into the canal of Schlemm. In one of my first papers I advised this procedure, and I still recommend it. It is really a goniotomy added to peripheral iridotomy. However, in most cases the cutting of the pectinate ligaments is not necessary.

SUBCONJUNCTIVAL DRAINAGE

When drainage from the posterior to the anterior chamber is insufficient after iridotomy,

the second type of operation that appeals to me is some form of subconjunctival drainage to be done through sclerectomy. Nearly every type of sclerectomy may give good results if the sclerectomy hole is bathed in aqueous, if done in an eye that is not inflamed, and the patient not too young. I think it is worth repeating that the sclerectomy hole in the young or in the inflamed eye tends to close. Every eye surgeon is acquainted with the various types of sclerectomy operations. They all depend on drainage into the subconjunctival tissue. I hold that this loose tissue under the conjunctiva is not structureless, but is designed to carry off fluid in a well-defined, apparently structureless, network which in my opinion should be left as much undisturbed as possible by any operation involving drainage under the conjunctiva.

Figures 6 through 10 present a modification of the Elliott sclerectomy. Instead of dissecting the conjunctiva from above, as in the various subconjunctival drainage operations, a slit is opened at an angle as shown in the drawing and the subconjunctival tissue is disturbed as little as possible. If the lymph spaces in the subconjunctival tissue are roughly broken down, they will, on healing, cause adhesions. The



MODIFICATION
OF THE
ELLIOTT SCLERECTOMY

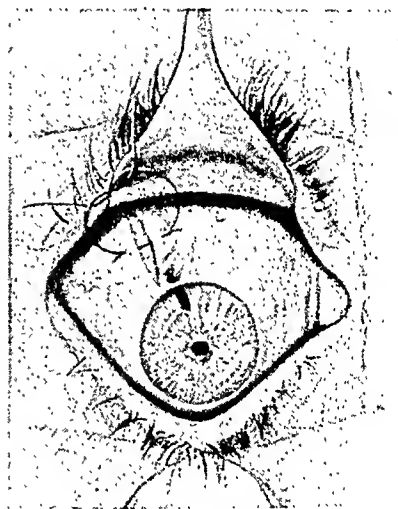
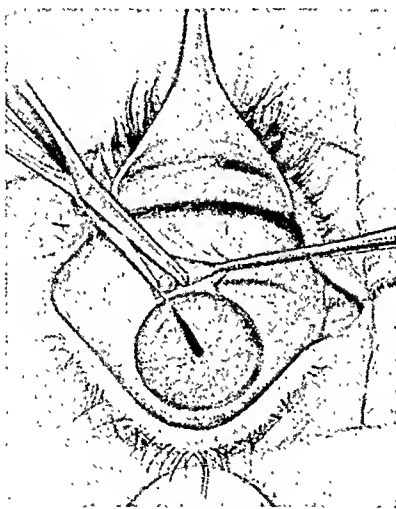


Figure 6 (top, left). The conjunctival incision and the dissection down to the cornea by a spatula in order to clear a small space at the junction of the conjunctiva with the corneal epithelium for the purpose of entering the anterior chamber with a trephine. Figure 7 (top, center). The trephine is in place, but it should be held at right angles to the plane of the disc to be removed. The picture does not show this clearly. The trephine should be so sharp that it cuts through the whole disc without any ragged ends. Figure 8 (top, right). If the disc is not cut through on all sides it may be necessary to cut some of the remaining fibers holding it. Figure 9 (bottom, left). The iris bulges up into the sclerectomy hole and an iridectomy or iridotomy should be done. The picture shows an iridotomy. Figure 10 (bottom, right). The finish of the operation. The iris has fallen back into its place and the conjunctiva is closed with one suture.

trephine hole is made as shown in the figures and the slit in the conjunctiva is closed with one stitch. The aqueous passes into the almost undisturbed subconjunctival tissue and after the wound is healed, there will be no unsightly bleb dissecting the corneal epithelium down-

ward, or raising a large conjunctival bleb upward. The aqueous flows into the tissue and passes off into the general circulation.

This modification is more difficult and requires more skill on the part of the surgeon than any other form of sclerectomy for the re-

lief of glaucoma. The trephine disc must be taken out in a smaller space; the iris will bulge in the sclerectomy hole and the iridectomy or iridotomy must be performed in a smaller space, but the operation results in longer lasting benefits to the patient.

IRIDECTOMY

THIS is the oldest operation for glaucoma. Von Graefe performed iridectomy for glaucoma before there was adequate general or local anesthesia. At that time, it was the greatest advance in the treatment of glaucoma. With this operation, which consists of removal of part of the iris, perhaps 25 to 30 per cent of cases can be relieved, and some can be cured. It is unnecessary to go into detail on the technic of this operation, as it may be found in every good text book on the subject.

There have been many modifications of the iridectomy operation. When it failed some thought that the failure was due to the fact that the iris was not cut far enough back to its roots. These writers advocate tearing the iris from its moorings, hoping to connect the spaces of Fontana more directly with aqueous in the anterior chamber. In late cases, where the roots of the iris adhere to the pectinate ligaments back of the cornea, this would be futile. Others thought that the iris should be included in the corneal wound, and hence we have iridotaxis and other iris-including operations. Including the iris in the wound supposedly enables communication between the anterior chamber and the subconjunctival spaces, and it does so for a time; eventually, however, especially in young patients, there is a return of glaucoma.

I have great respect for iridectomy in its proper place. I do not think that its modifications have added to its value. Its real value is that it establishes a direct communication between the posterior chamber and the anterior chamber. Peripheral iridotomy is a better and safer way of making a direct communication from the posterior to the anterior chamber. It does all that iridectomy does without the dangers involved. Producing a subconjunctival

filtration with an iridectomy is a different operation; it is an iridectomy combined with subconjunctival filtration, which acts very well in some cases.

CYCLODIALYSIS

This is a comparatively modern operation recommended for glaucoma following cataract extraction. It has been used in congenital glaucoma, which is a phase of chronic primary glaucoma, according to my definition. I should like to say more about the indications for this operation, but the scope of this address does not include it as a possible operation for ordinary chronic primary glaucoma with its exacerbations, except for its doubtful benefit in infantile congenital glaucoma. Cyclodialysis provides an exit of the aqueous into the choroidal spaces where it is taken up by choroidal capillaries and returned into the venous circulation through the choroidal capillary veins. In my experience, it has been successful for the first month or so, but an abject failure thereafter.

CONIOTOMY

Goniotomy is still in its experimental stage. It is an attempt to open the spaces of Fontana by cutting the pectinate ligaments. In my first description of the peripheral iridotomy operation in 1920, I advised an attempt to cut through the pectinate ligaments. I still do.

As you will observe, all these operations attempt to provide a free exit of fluid from the eye. In 1923 I began to work on the problem of preventing, by operation, too much formation of aqueous. I was attracted by some experiments of Dr. L. Post of St. Louis, in applying measured heat through the Shahan thermophore to the ciliary region. He succeeded in reducing intraocular pressure in some cases. In 1925 I read a paper at the New York Academy of Medicine describing subconjunctival cauterization of the ciliary body with the objective of decreasing the amount of aqueous by putting the secreting cells of the ciliary body and the capillaries supplying them out of commission.

All other operative efforts previous to this were designed to provide a greater exit of the aqueous from the eyeball; none were designed to lessen the production of aqueous. More recently diathermy has been applied subconjunctivally to decrease aqueous production. Perhaps this is an improvement over my subconjunctival actual cautery.

As one of the pioneers for the prevention, by operation, of more aqueous production, I feel a responsibility to advise caution in this direction. Such operations should be used only as a last resort. They produce too much scar tissue, and if they fail, no subsequent filtering operation may be successful. Cyclodialysis in the same region would also be futile; I have used it only in blind eyes. More work should be done in this direction before the operation is done on seeing eyes. At present I advise, as I did in 1925, its use in hopelessly blind eyes just to save the eyeball. There may, however, be a better future for this type of operation. A great deal of research may disclose useful information as to control of the production of aqueous both by operation and application of newer drugs.

ANATOMIC CLASSIFICATION OF CHRONIC PRIMARY GLAUCOMA IN SELECTING CASES FOR PERIPHERAL IRIDOTOMY

MOST cases of chronic primary glaucoma in adults fall into the following types: (I am omitting megalophthalmos anterior, and buphthalmos. They appear in infancy and childhood, but still are included in the class of chronic primary glaucoma.)

Type 1—The first type of glaucoma is that which is often encountered in the Negro race, in which we find the chief characteristics to be a small cornea, a moderately shallow anterior chamber, and a thick, brown iris which does not show much, if any, contour of the crystalline lens because of the small diameter of the cornea. This type is not entirely suitable for peripheral iridotomy for glaucoma except as a preliminary to later, more radical operation. It is more suitable to some form of sclerectomy.

Type 2—In the second type, we find a deep

or a normal anterior chamber, and a normal or a large cornea. The obstruction in these cases is at the filtering angle. The iris is not usually thin but is often brown and bulky. There may be poor response to miotics, but not always. Probably the chief mechanical cause here is not a lack of drainage through the pupil to the anterior chamber, but a congenital limitation of the entrance of the canal of Schlemm or a tendency to close the angle of filtration by a bulky iris, or even a small canal leaving an exit capable of dealing with a normal production of aqueous, but incapable of dealing with any increased production or a later normal rise and fall. In these cases, even when far-advanced, there is little decrease in the depth of the anterior chamber. The margin of safety here is small, and drainage through the sclera to the subconjunctival tissue may be indicated. Iridotomy gives temporary relief in this type, and is suitable only in preparation for a more radical operation, such as a properly performed sclerectomy. Sclerectomy should not be done while the puncture through the sclera is still bathed in aqueous. Iridectomy in such cases does no more than an iridotomy, but with greater danger, and neither is sufficient. This type calls for some form of subconjunctival drainage.

Type 3—In the third type, we find a small or normal cornea with a shallow anterior chamber, and an iris with small, nodular enlargements or a congenital network of iris tissue attached far out from the limbus in the cornea (faulty development of the iris and anterior chamber). This tends to choke the filtering angle even with the pupil contracted. The iris, however, does not bulge forward, nor does it show the contour of the lens to any great extent. If there is any forward movement or bulging of the iris, it is obscured by the peculiar formation of the iris at its attachment. Miotics bring down the pressure fairly well in the earlier stages, so it would seem that the entrance of the canal of Schlemm is in good order, and its capacity to take up the fluid not impaired if the base of the iris could be thinned out with a miotic to open up the angle. One chief mechanical trouble here is the thick base of the iris

with the small filtering angle, coupled, perhaps, with a small margin of safety as to the exit through the canal of Schlemm. The margin of safety being small, a peripheral iridotomy gives temporary relief, and sometimes helps the miotic to do better work in preparation for a sclerectomy later, if necessary.

Type 4—In the fourth anatomic type of glaucoma, we find a marked bulging forward of the iris with the contour of the lens well-shown, a shallow anterior chamber, and usually a thin iris. The majority of these cases are in blue or gray eyes. The cornea may vary in size. In the earlier stages, these cases react well to miotics, but later, owing to adhesions of the iris over the pectinate ligaments or to the back of the periphery of the cornea, or adhesions of the iris to the anterior capsule of the lens caused by the prolonged use of miotics, they react poorly or not at all to miotics. Indeed, in late cases miotics may increase the intraocular pressure. When a good peripheral iridotomy is done in this type, it is a great relief to the surgeon to see the anterior chamber deepen, sometimes even on the operating table. This may happen whether it is an early case without peripheral adhesions or an older one.

Type 4 is the ideal type for peripheral iridotomy. Almost all the congestive cases are found in Type 4. In acute congestive cases with a pressure so high that it would be dangerous to do an iridectomy or sclerectomy, a peripheral iridotomy, if done in time, usually saves the eyesight. For these acute, painful cases, a general anesthetic should be used.

CONGESTIVE AND NONCONGESTIVE GLAUCOMA

I HAVE NOT tried to differentiate between congestive and noncongestive chronic primary glaucoma. It would appear that their relationship is purely anatomic. If there is a sudden rise of intraocular pressure, there will be so-called congestive signs and symptoms. Intraocular pressure in the normal eye varies during the day and the night and under such conditions as emotional stimulation, pleasant or un-

pleasant. An eye well balanced in structure can take care of these normal variations in the production of intraocular fluid which regulates the pressure, but in unusual vasomotor disturbances, this may not be the case. In some eyes, the increase of pressure may be so gradual that there may be no signs of congestion, even though the pressure may reach an extremely high point and blindness ensues. Again, a normal, or moderately high, intraocular pressure may go on without congestive symptoms until it produces blindness due to the weak structure of the lamina cribrosa, yet both of the above conditions are likely to produce congestive symptoms at any time if there is a sudden rise of pressure. The congestive symptoms depend on a sudden rise of intraocular pressure and are less likely to appear after iridotomy.

Nearly all of the so-called noncongestive glaucomata are of Types 1, 2, and 3. Because of their anatomic structure there may be no sudden increase of pressure, and no congestive symptoms. Very rarely do we find a noncongestive one among Type 4 cases. Therefore, it would appear that the noncongestive and congestive glaucomas depend on the difference in the structure of the eye, modified, of course by the nervous stability of the patient. The eyes in Type 4 furnish nearly all the congestive and acute cases of chronic primary glaucoma due to certain structural features, such as the bulging iris closely adapted to the lens, but not necessarily adherent to the lens. After peripheral iridotomy, the congestive symptoms disappear, and if the margin for safety in the rise and fall of the production of intraocular fluid is not great enough at the filtering angle, it may appear later as a noncongestive glaucoma or, less likely, a congestive one. Thus, with an alteration in structure by operation, the congestive type is turned into the noncongestive type. This proves that the congestion or so-called inflammation seen in the acute attacks is not the cause, but the result of the sudden high pressure, and is not due to any disease or toxic agent. While it is conceivable that allergy may, in isolated cases, be a potent factor, I have had no such cases in my experience.

Radioactive Iodine in the Study and Treatment of Thyroid Diseases

F. RAYMOND KEATING, JR.*

MAYO CLINIC, ROCHESTER

THE DISCOVERY of radioactive isotopes and their production in quantity in the cyclotron and in the chain-reacting uranium pile has provided the physiologist and physician with new tools for the study of metabolic processes in health and disease. The application of these strange and dangerous products of nuclear physics to the biologic sciences has been likened in importance to the discovery of the microscope.

Among the first radioactive isotopes to be prepared artificially was an isotope of iodine.¹ Because of the specific affinity of the thyroid gland for iodine and the specific role of iodine in the formation of thyroid hormone it is not surprising that radioactive isotopes of iodine have been applied promptly and widely to the study of thyroid physiology and thyroid disease. The first such study began in 1937 as a cooperative investigation in the Physics Department of the Massachusetts Institute of Technology and the Thyroid Clinic of the Massachusetts General Hospital; soon thereafter a

similar project was initiated at the University of California.

Many investigators in other institutions have since employed similar technics for the study of problems related to the thyroid. In the laboratory these studies have been done on animals, normal human beings, and with *in vitro* technics on sections of thyroid tissue. In the clinic and at the bedside radioiodine has been applied to the study of patients suffering from various thyroid disorders. In addition, a start has been made in the evaluation of radioiodine as a therapeutic tool.

For the proper appreciation of these accomplishments, their limitations, their significance, their present value, and their possible extension in the future, some digression to describe the basic physical characteristics of radioactive isotopes is necessary. The wedding of nuclear physics and the medical sciences imposes on investigators and clinicians a new discipline, complete with new materials, new instruments, new units of measurements, new terms and concepts, and new and terrifying hazards. For a thorough exposition of this subject in its more general aspects the reader is referred to the excellent discussion by Lawrence.²

*Division of Medicine, Mayo Clinic, Rochester, Minnesota

Presented before the meeting of the Interstate Postgraduate Medical Association of North America, St. Louis, Missouri, October 14 to 17, 1947.

THE NATURE OF RADIOACTIVE ISOTOPES OF IODINE (RADIOIODINE)

The word "isotope" refers to forms of the same element which have different atomic weights. More than twelve isotopes of iodine have now been described, but only one, I^{127} (iodine of atomic weight 127), occurs in nature. The others are prepared by various means in the cyclotron or the chain-reacting pile,² or result as fragments of the fission of uranium or plutonium.⁴ In addition to the difference in atomic weight, all isotopes of iodine excepting I^{127} are radioactive, which means that they emit rays of various types not unlike some of the radiations from radium and its disintegration products.

A radioactive isotope is unstable, since, as each atom emits radiation, it disintegrates into something else, so that any given stock of the isotope gradually diminishes in quantity. The time required for half of any given quantity of a radioactive isotope to disappear is called its "half-life." Each type of radioactive isotope has a characteristic type of radiation and a definite half-life, and it is customary to designate particular isotopes either in terms of their atomic weight or their half-life.

The first isotope of iodine used in the study of thyroid function was I^{128} with a half-life of twenty-five minutes.⁵ Because of its brief half-life I^{128} imposed a crippling time limit on the duration of observations. In later investigations both on laboratory animals and on human beings, a mixture of I^{130} and I^{131} with half-lives of 12.6 hours and 8.0 days respectively was employed. This mixture, which was about 90 per cent I^{130} and 10 per cent I^{131} , resulted from the bombardment of tellurium by deuterons in the cyclotron. Recent studies have utilized exclusively I^{131} in pure form, obtained by the bombardment of tellurium with slow neutrons; the chain-reacting pile has been used as a source of neutrons. The source and fate of I^{131} is shown diagrammatically in Figure 1.

THE RADIATION OF RADIOIODINE

The isotopes of iodine most frequently em-



F. RAYMOND KEATING, JR.

ployed (I^{130} and I^{131}) are alike in that both emit both beta particles and gamma rays. A beta particle is a negative electron which travels at high speed. This form of radiation is rapidly absorbed by surrounding material and hence can traverse at most only a few millimeters of tissue. The gamma ray on the other hand is not a particle in the usual sense, but is an electromagnetic wave, or photon, similar to visible light or to the roentgen ray, but of much shorter wavelength than most roentgen rays. Gamma rays travel at the velocity of light, are not readily absorbed by surrounding material and hence can penetrate a much greater distance in tissue or in air than can beta rays.

As radiation of any form passes through any material, including tissue, it imparts its energy to the material until its energy is entirely absorbed. Most of the energy so imparted produces ionization of the material, as individual molecules are split into ion pairs consisting of positively charged and negatively charged particles. Beta radiation is quickly absorbed and

The Source and Fate of Iodine 131

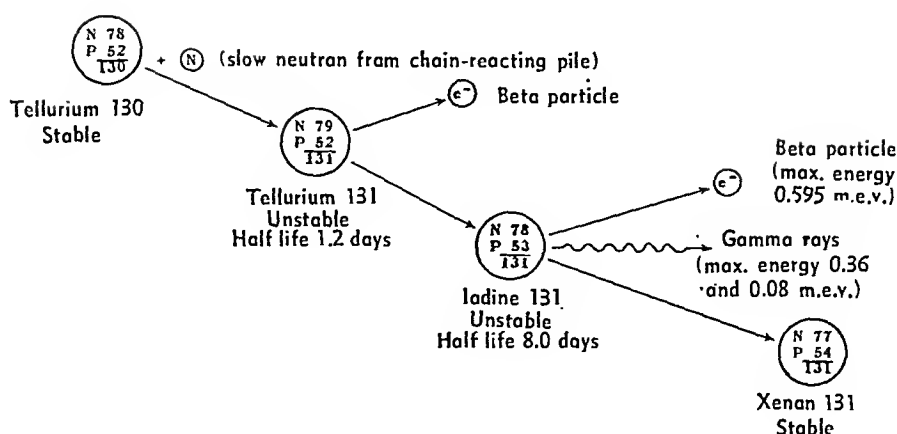


Figure 1. Diagram showing the radioactive chain of which I^{131} is a part. Each large circle represents a nucleus and the figures within each circle indicate the composition of the nucleus. *P* indicates the number of protons (particles having the mass of a hydrogen nucleus and bearing a positive charge). *N* indicates the number of neutrons (particles having the same mass as protons but no charge). The sum of protons and neutrons determines the atomic weight. The number of protons equals the atomic number and hence defines the chemical identity of the isotope. The chain is started by bombardment of stable tellurium¹³⁰ with slow neutrons.

hence produces a considerable quantity of radiation within a short space. Gamma radiation is not readily absorbed and hence within a short space produces much less ionization than beta rays.

The amount of ionization which a particular radiation can cause in a given space depends in part on the energy which it contains. The energy contained in radiation is measured in million electron volts (m.e.v.) and the radiations of each isotope are characterized by specific maximal energies. For example, the beta particle of I^{131} has a maximal energy of 0.595 m.e.v. and its two gamma rays have maximal energies of 0.365 and 0.080 m.e.v. respectively.

Radiation from radioiodine produces effects on tissues similar to those produced by roentgen rays. Since the biologic effect of any radiation on tissue probably results largely from ionization, the beta radiation of radioiodine in tissue may account for 99 per cent of its biologic effect. Gamma rays in large amounts may pro-

duce similar effects and in view of their great penetration constitute a hazard to the user.

Precautions similar to those used by roentgenologists must be employed by persons working with radioiodine. Large quantities of radioiodine are present in the urine of patients taking it and the handling and disposal of the urine of patients treated with radioiodine are problems of importance. Proper shielding of those working with any radioactive material is essential. Measurement of individual exposure of radiologists, physicians, and technicians by means of film badges or small electroscopes should be carried out at frequent intervals.

THE MEASUREMENT OF RADIOIODINE

The radiation of radioiodine or of other radioisotopes, is most commonly detected by the ionization it produces. A number of instruments have been devised for the measurement of this ionization, including various types

of electrometers, electroscopes, and ionization chambers. However, for practical purposes the measurement of radioisotopes in medicine and biology has come to depend largely on the use of the Geiger-Müller counter. When this instrument is connected with an electronic counting device, exceedingly minute amounts of radioactive material may be measured with speed and with satisfactory accuracy.

In most instances a Geiger-Müller tube is employed which is specifically constructed for the particular type of radiation to be measured; in the case of radioiodine either beta-ray counters or gamma-ray counters are employed; the counter used depends on the specific problem to be met. Accurate measurement of radio-

activity requires meticulous care and great vigilance. The geometry of the apparatus, the physical characteristics of the isotope, the efficiency, and stability of the detecting instrument must all be considered and in addition account must be taken of such factors as cosmic rays, natural radioactivity in common materials, and other stray sources of radiation measured together as "background count."

A quantity of a radioisotope is measured in terms of its radiations. The unit of measurement is the curie, originally defined as the amount of radon in equilibrium with a gram of radium. To extend its use to other substances the curie has been redefined as 3.7×10^{10} (37,000,000,000) disintegrations per second.

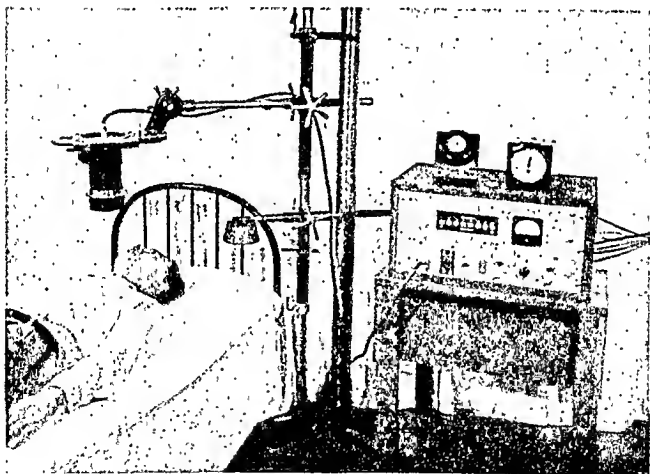


Figure 2. The measurement of I^{131} *in vivo* with a Geiger-Müller counter. The subject reclines on a hard bed; the Geiger-Müller tube heavily shielded in lead is fixed in position over the neck. The gamma radiation from the thyroid detected by the tube is automatically recorded and counted in the scaler on the right. After a satisfactory reading is taken, a thick lead plug is interposed between the window of the counter tube and the subject and a second reading is made. The second reading is used to correct for radiation entering the tube from sources other than the target. Measurements so obtained are expressed in "counts per second." Before they can be expressed as microcuries of radioiodine comparison must be made with a standard of I^{131} , taking account of radioactive decay, geometric relationships and other factors, such as absorption and scatter by the tissues interposed between thyroid and tube.

The Source and Fate of Iodine 131

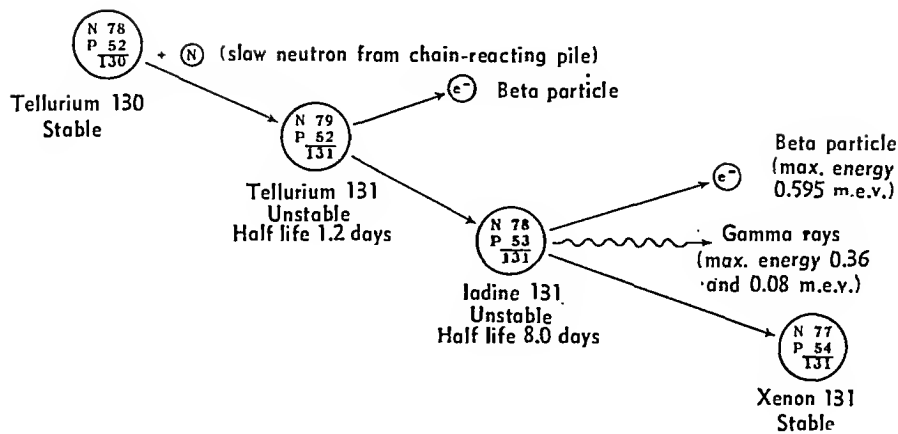


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treatment with thiocyanates⁹ were among the factors which increased affinity of the thyroid for the radioiodine. The previous administration of iodine¹² or thyroxin and hypophysectomy^{9, 13} were some factors which helped to reduce it. Thiouracil and related goitrogens promptly and markedly decreased the collection of radioiodine by the thyroid before any other effects of these agents were evident.¹⁴ McGinty and Rawson¹⁵ have used this property to appraise the antithyroid potency of numerous drugs of the thiourea and aniline series, while Keating, Rawson, Peacock and Evans¹⁶ have studied the collection and secretion of radioiodine by the chick thyroid in an attempt to elucidate the mode of action of pituitary thyrotropic hormone.

Perlman, Morton and Chaikoff^{17, 18} have used radioiodine in *in vivo* and *in vitro* studies to examine the rate and mode of formation of diiodotyrosine and thyroxin by thyroid tissue. Recently, Taurog, Chaikoff and Entenman,¹⁹ using a rather indirect method, have employed radioiodine to determine the turnover rate of protein bound ("hormonal") iodine in the plasma of dogs.

APPLICATION OF RADIOIODINE TRACERS TO THE STUDY OF THYROID DISEASE

While its use in studies of laboratory animals has been productive, radioiodine may prove even more useful in the investigation of thyroid function in man. Its use makes possible the quantitative examination of numerous aspects of iodine metabolism and thyroid function in the intact human being which cannot be approached by other means. This field was first explored by Hamilton and Soley,²⁰ who studied the collection of ingested radioiodine in the thyroid and its excretion in the urine and feces. Similar studies have been carried out by Hertz and his associates,^{8, 21} by Rawson and his co-workers^{22, 23} and by Keating, Power, Berkson and Haines.²⁴

The disposal of a tracer dose of radioiodine may be followed in several ways. Its collection in the thyroid can be measured *in vivo* by serial

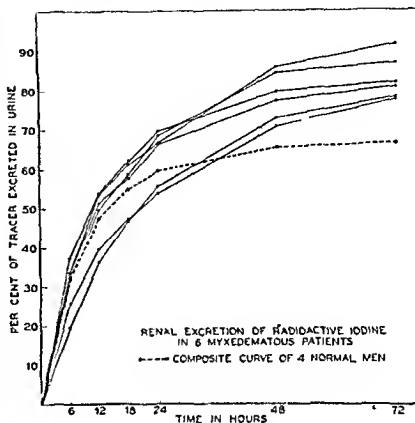


Figure 4. Urinary excretion of radioiodine by 6 patients with myxedema. More radioiodine appeared in the urine than in that of normal persons and excretion persisted for a longer time. The dashed line is the composite urinary excretion curve of four normal persons for whom data are shown in Figure 3.

measurements over the thyroid region with a Geiger-Müller, gamma-ray counter (Figure 2). Excretion in the urine may be determined by measuring the radioactivity in the urine pooled for twenty-four or forty-eight hours. More detailed information can be obtained by carefully collecting urine for shorter intervals and measuring radioactivity in each collection.²⁵

The disappearance of radioiodine from the blood can be calculated from curves constructed from observations of the thyroid or the urine, or can be determined directly from a series of samples of plasma. Very similar information can be obtained *in vivo* by applying a gamma-ray counter to some peripheral portion of the body such as the thigh.²⁴

Radioiodine can be measured with speed and accuracy in urine without treating it chemically. The problems of preparation of material, absorption of radiation and so on make measurement of radioiodine in blood and excised tissue more difficult. *In vivo* measurements of radioiodine present still further difficulties and

A millicurie is 0.001 curie (3.7×10^5 disintegrations per second) and a microcurie is 0.001 millicurie (3.7×10^4 disintegrations per second). With an efficient Geiger-Müller tube designed to detect beta rays I^{131} may be measured with reasonable accuracy in quantities as small as 30 disintegrations per second (about 0.001 microcurie).

Even a substantial quantity of I^{131} in terms of radiation represents an incredibly minute quantity in terms of weight. For example, 10 millicuries, a quantity definitely in the therapeutic range, giving off 370,000,000 disintegrations per second, weighs approximately 0.08 micrograms. Most investigations have employed quantities of radioiodine of the order of 1 to 10 microcuries for studies in small animals; for tracer studies on human beings 100 microcuries generally have been employed.

RADIOIODINE TRACERS

The great usefulness of radioiodine resides in the fact that it is chemically and physiologically identical with natural iodine, providing it is present in quantities sufficiently small as to be without biologic effects due to radiation per se.* In small quantities radioiodine can be used as a tracer or tag for the study of various aspects of iodine metabolism and thyroid function. Since the quantities of radioiodine which can be detected are exceedingly minute, it may be used to observe metabolic reactions in conditions of physiologic equilibrium.

The quantity of radioiodine required for a tracer is so small, that it is often mixed with a measured amount of inert natural iodine, called a "carrier." Since the stable iodine and radioiodine so mixed are chemically and biologically identical, the radiation subsequently measured may be regarded as labeling both the radioiodine and the inert carrier iodine as well. If desired, radioiodine may be given without carrier and when so used it can be regarded as

labeling all of the iodine in similar chemical form in the organism without measurably increasing the stock of such iodine already present. Carrier-free tracers of radioiodine may be subject to serious inaccuracies owing to loss of part of the minute amount of iodine on the walls of containers or pipettes.

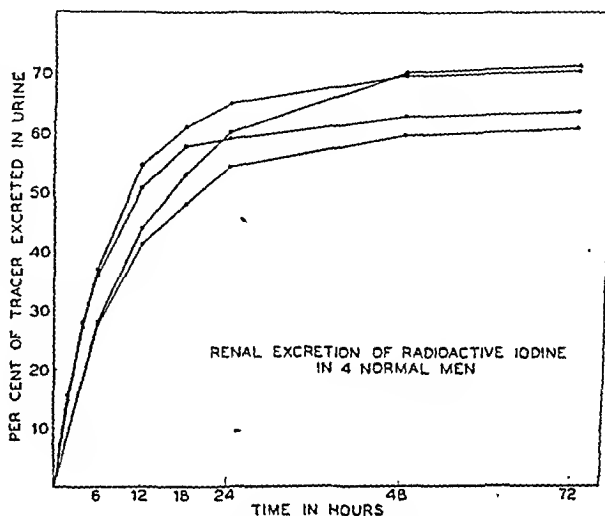


Figure 3. Urinary excretion of radioiodine by normal persons. The curves have the same form and reach a plateau at about the same time, as do the curves in Figure 6 indicating collection of radioiodine by the normal thyroid.

LABORATORY STUDIES WITH RADIOIODINE

An excellent review of the numerous important applications of radioiodine to study of thyroid physiology has been published recently by Rawson and McArthur.⁶ The following summary serves only to indicate the scope and versatility of the tracer technic when applied to thyroid problems. Hertz and his associates,^{5, 7, 8} LeBlond and Sue,⁹ Ariel and co-authors¹⁰ and others have observed that the thyroid collects much larger quantities of administered radioiodine than do other tissues, and that variations in the avidity of thyroid for iodine could be correlated with various histologic and physiologic states of the gland.

Iodine deficiency,¹¹ soy bean diet,¹² and

*Fortunately, unequivocal evidence of biologic effects from small doses has not been found, but in nearly all tracer studies it is exceedingly difficult to be certain that the provision of no biologic effects due to radiation has been met.

treatment with thiocyanates⁹ were among the factors which increased affinity of the thyroid for the radioiodine. The previous administration of iodine¹² or thyroxin and hypophysectomy^{10, 13} were some factors which helped to reduce it. Thiouracil and related goitrogens promptly and markedly decreased the collection of radioiodine by the thyroid before any other effects of these agents were evident.¹⁴ McGinty and Rawson¹⁵ have used this property to appraise the antithyroid potency of numerous drugs of the thiourea and aniline series, while Keating, Rawson, Peacock and Evans¹⁶ have studied the collection and secretion of radioiodine by the chick thyroid in an attempt to elucidate the mode of action of pituitary thyrotropic hormone.

Perlman, Morton and Chaikoff^{17, 18} have used radioiodine in *in vivo* and *in vitro* studies to examine the rate and mode of formation of diiodotyrosine and thyroxin by thyroid tissue. Recently, Taurog, Chaikoff and Entenman,¹⁹ using a rather indirect method, have employed radioiodine to determine the turnover rate of protein bound ("hormonal") iodine in the plasma of dogs.

APPLICATION OF RADIOIODINE TRACERS TO THE STUDY OF THYROID DISEASE

While its use in studies of laboratory animals has been productive, radioiodine may prove even more useful in the investigation of thyroid function in man. Its use makes possible the quantitative examination of numerous aspects of iodine metabolism and thyroid function in the intact human being which cannot be approached by other means. This field was first explored by Hamilton and Soley,²⁰ who studied the collection of ingested radioiodine in the thyroid and its excretion in the urine and feces. Similar studies have been carried out by Hertz and his associates,^{8, 21} by Rawson and his co-workers^{22, 23} and by Keating, Power, Berkson and Haines.²⁴

The disposal of a tracer dose of radioiodine may be followed in several ways. Its collection in the thyroid can be measured *in vivo* by serial

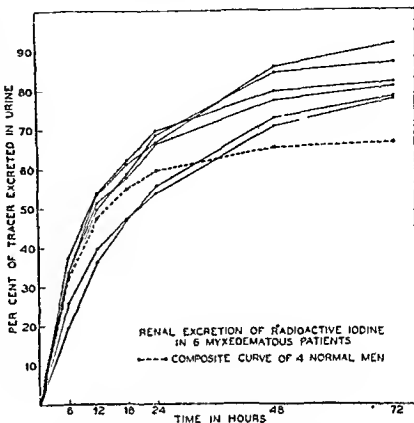


Figure 4. Urinary excretion of radioiodine by 6 patients with myxedema. More radioiodine appeared in the urine than in that of normal persons and excretion persisted for a longer time. The dashed line is the composite urinary excretion curve of four normal persons for whom data are shown in Figure 3.

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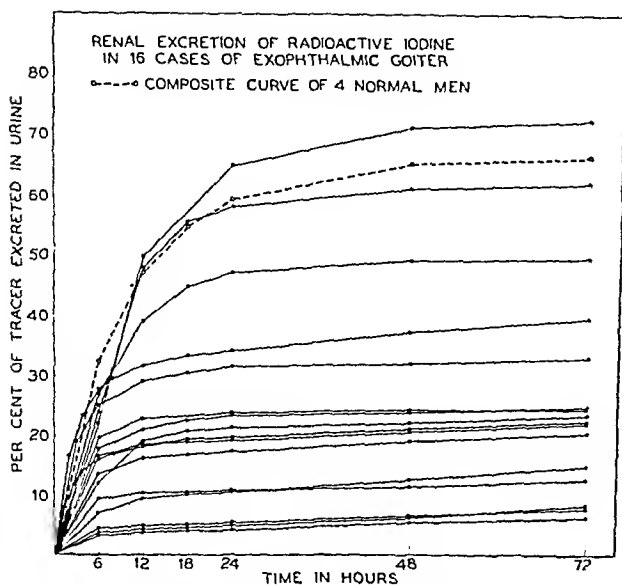


Figure 5. Urinary excretion of radioiodine by 16 patients with exophthalmic goiter. The dashed line is the composite curve of the four normal persons on whom data are shown in Figure 3. In all except three of the cases of hyperthyroidism excretion of radioiodine fell below the normal range. Less radioiodine is excreted in cases of hyperthyroidism and urinary excretion of radioiodine is essentially complete in a much shorter period of time than among normal persons.

with present methods can be regarded as no more than close approximations. When it becomes possible to make several or all of the foregoing types of observations simultaneously with satisfactory accuracy, a rather complete quantitative analysis of the dynamics of iodine metabolism in a given patient will be quickly available.

An oral dose of radioiodine is rapidly absorbed from the gastrointestinal tract. By applying a counter over the hand, Hamilton²⁶ was able to show that absorption was 80 per cent complete within an hour. Radioiodine may be detected in the thyroid gland and in the urine within ten minutes of the time it is swallowed. Hamilton and Soley²⁷ found insignificant amounts (about 1 per cent) in the feces; most of an ingested or injected dose is either collected by the thyroid or excreted in the urine. A variable quantity, 5 to 15 per cent

of the dose, cannot be accounted for and may be diffusely stored in other tissues.

BY ALL of the methods of measurement which have been mentioned, important differences are found in the behavior of tracers in various thyroid states. With tracers consisting of 100 microcuries of I^{131} in 100 micrograms of sodium iodide added as carrier, normal persons excrete an average of 65 per cent of the dose in the urine (Figure 3). The curve of urinary excretion levels off after about twenty-four to thirty-six hours. Hypothyroid patients (Figure 4) excrete 85 to 90 per cent of the dose, and urinary excretion continues for four to six days. Hyperthyroid patients excrete generally less than normal persons, sometimes as little as 5 per cent of the dose, and the curve of urinary excretion levels off much more quickly, sometimes within three to six hours (Figure 5).

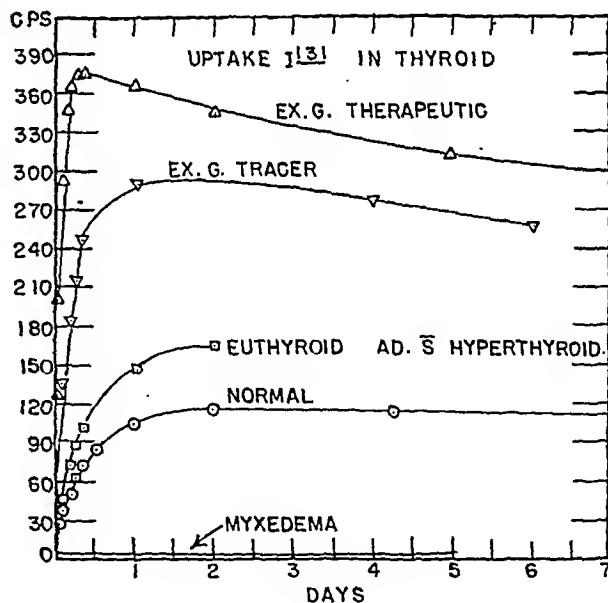


Figure 6. Collection of radioiodine tracers by the thyroid in various thyroid states. Representative curves are shown. For purposes of comparison between individuals receiving different doses of I^{131} the radioactivity in the thyroid is expressed as counts per second per millicurie.

(Published through the courtesy of Dr. T. J. Luellen)

In vivo measurements of the collection of radioiodine in the thyroid give substantially the same results (Figure 6*); normal thyroid glands collect 20 to 30 per cent of the dose, and collection levels off in about twenty-four hours; hyperthyroid glands collect more than normal glands and they do so more quickly; hypothyroid glands collect little if any. Hamilton and others²⁸ observed two hypothyroid children whose goitrous thyroids had collected temporarily large amounts of an ingested dose. When the blood is examined it is found that radioiodine disappears from the blood of hyperthyroid individuals more quickly, and from the blood of hypothyroid patients less quickly, than from the blood of normal subjects (Figure 7).

Keating and associates²¹ have shown that it is possible by mathematical analysis of the curves obtained to determine the rates at which iodine is being collected by the thyroid, excreted by the kidney or withdrawn from the blood. These rates may prove to reflect the physiologic state of affairs more faithfully than the measurements of absolute amounts.

RADIOIODINE tracers may have some value as diagnostic aids. The behavior of a tracer in a hyperthyroid individual is usually distinctive. As might be expected, however, some definitely hyperthyroid patients have made a normal response. In at least one instance such an anomalous result has provided the first inkling that the hyperthyroidism was the result of ingestion of desiccated thyroid. More experience with the iodine tracer method in other conditions than hyperthyroidism is necessary before the diagnostic value of tracer studies can be accurately appraised.

Following ingestion of Lugol's solution, patients who have hyperthyroidism may give a normal or even a hypothyroid type of response. Rawson²² has found that patients taking thiouracil or related compounds excrete substantially all of the radioiodine in the urine.

*The studies illustrated in Figures 6, 7 and 8 are to be published in collaboration with various members of the radioiodine study group of the Mayo Foundation.

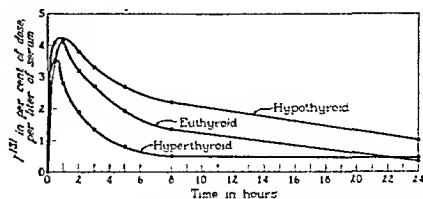


Figure 7. Composite curves of concentration of radioiodine in plasma in various thyroid states. Radioiodine disappears from blood more slowly in presence of hypothyroidism than in normal states and more quickly in presence of hyperthyroidism than in normal states. The rate of disappearance of radioiodine from blood may be calculated indirectly from curves of urinary excretion or collection in thyroid.

(Published through the courtesy of Dr. W. M. McConehey)

Stanly and Astwood²⁹ have used the collection of radioiodine by the thyroid gland of human beings as the basis for appraising the relative activities of various antithyroid compounds.

Tissue analysis and autoradiograms.—Radioiodine also may be employed in the study of thyroid tissue removed at operation. If a patient is given a tracer a day or more preceding operation, the surgical specimen may be analyzed for its radioiodine content. Hertz, Roberts and Salter³ treated such specimens of thyroid chemically by extracting the diiodotyrosine and thyroxine-like material which they contained, and showed that with increasing intervals after the administration of radioiodine the proportion of the radioiodine in the thyroxine fraction increased.

McArthur and Cope²⁰ administered radioiodine preoperatively to 18 patients with discrete nodules of the thyroid and compared the radioactivity of digests of the tumor tissue with digests of the adjacent uninvolved tissue. Undifferentiated nodules collected much less than the adjacent normal tissue; well-differentiated nodules often collected more than the surrounding tissue. In cases of toxic adenoma, nearly all of the radioiodine collected was in the adenoma with little or none in the extra-adenomatous tissue. LeBlond and his collab-

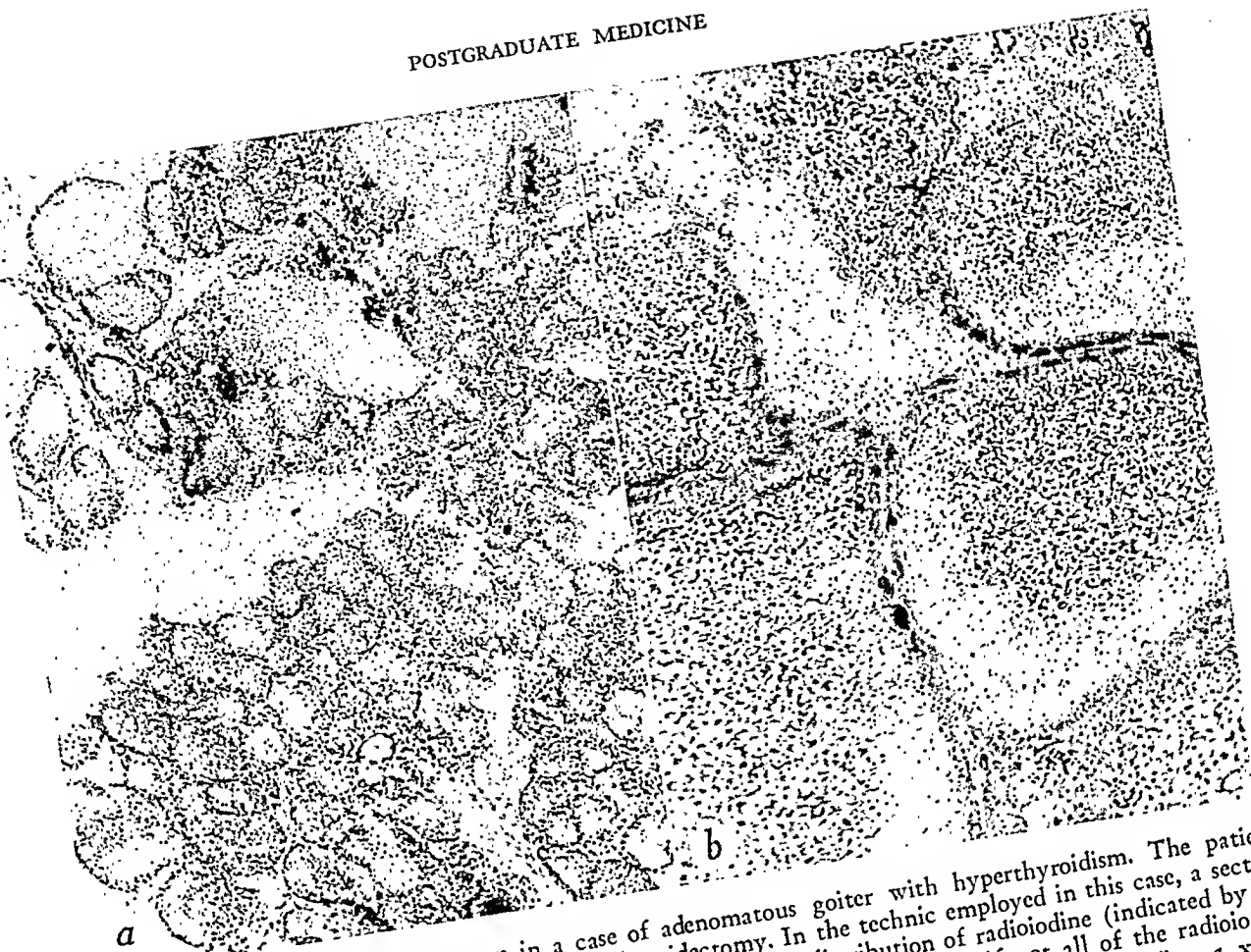


Figure 8a and b. Autoradiogram in a case of adenomatous goiter with hyperthyroidism. The patient received a tracer dose of I^{131} two days before thyroidectomy. In the technic employed in this case, a section of tissue and sensitized emulsion were superimposed, so that the distribution of radioiodine (indicated by the black silver granules) is seen against the background of thyroid structure. Most if not all of the radioiodine was deposited in the colloid. Different follicles contained varying concentrations of the radioiodine. a, x 80; b, x 300.

(Published through the courtesy of Dr. W. C. Pratt.)

orators³¹ on the other hand found thyroid adenomas to be functionally less active than the surrounding normal tissue as shown by a lower radioiodine content, as well as by a smaller proportion of radioiodine converted to diiodotyrosine or thyroxine.

Hamilton, Soley and Eichorn³² pioneered in applying the technic of autoradiography to the study of thyroid tissue. An autoradiogram is made by applying a photographic emulsion to a microscopic section of thyroid tissue which previously had collected radioiodine. The resulting pattern or autoradiogram discloses the distribution and density of the radioiodine in the tissue (Figure 8a and b). Autoradiograms have proved useful in the study of thyroid

nodules and thyroid neoplasms. They provide pathologists with an unexcelled opportunity to correlate histologic structure with function. By this means most thyroid carcinomas can be shown to collect very little iodine. One striking feature disclosed by autoradiograms of adenomatous goiters is the great disparity in function between different follicles within the same thyroid gland. Some follicles show dense concentrations of the radioiodine while others show comparatively little.

Radiation effects—In interpreting radioiodine tracers investigators must always consider the possible presence of effects due to radiation per se. The remarkable capacity of the thyroid to concentrate and store iodine—the very property

which makes radioiodine a useful tool—makes it difficult to avoid in the thyroid radiation theoretically sufficient to exert a biologic effect. The resolution of this problem is hindered by the fact that no one knows what to regard as the upper limit of safety in exposure to radiation.

Until recently workers with roentgen rays and radium have been advised to limit total exposure of the body or any part to less than 0.1 r per day. More recent standards have set the permissible limit of exposure at 0.01 r per day. No data have been obtained which would even suggest what the limit should be for internal radiation of a tissue, such as the thyroid, by a radioisotope incorporated in its substance, but there is at least no reason to suppose that a level higher than the foregoing should be chosen arbitrarily.

IN ALL of the tracer studies thus far reported, whether on animals or human beings in which calculations may be made, such arbitrary tolerance doses are substantially exceeded in the thyroid. The standard quantity of I^{131} which we at the clinic have employed in clinical studies with tracers is 100 microcuries. Assuming a thyroid gland of normal size and with normal capacity to collect iodine, such a tracer will produce a concentration of radioiodine of about 1 microcurie per gram. This concentration of I^{131} in tissue will produce about 12 r of radiation per day and a total integrated dose of about 150 r, provided that all of the I^{131} stays in the thyroid until decay is complete.

To carry out a tracer study on human beings, which would not impose an exposure to radiation of more than 0.01 r per day on the thyroid would by the same calculations require a total oral dose of I^{131} of 0.1 microcuries! At present so minute a dose could be detected only with the greatest difficulty.

Fortunately, thus far there has been little evidence that the radiation produced by tracers of 100 microcuries is either injurious to the patient or capable of producing artefacts in the results.

Until positive information regarding radiation effects is available, however, it is most unwise to assume that radioiodine tracers are either entirely free of danger or entirely free of error on this score.

TREATMENT WITH RADIOIODINE

Radioiodine will probably find its chief use as a tool for the study of thyroid function. However, it also has some promise as a therapeutic agent. In 1942 Hamilton and Lawrence³³ reported that they had produced almost complete destruction of the thyroid in dogs and rabbits with I^{131} without evidence of damage to other tissues. These authors also reported preliminary observations made on three patients whose hyperthyroidism was treated with radioiodine. Hertz and Roberts³⁴ reported early results also in the treatment of exophthalmic goiter. While both groups were encouraged by their trials, they did not publish sufficient detail for an adequate appraisal of the procedure.

Hertz and Roberts³⁴ recently have reported a detailed follow-up study of their experience in treating twenty-nine patients. Owing to the fact that the patients were also given ordinary iodine, the results reported are difficult to interpret. Chapman and Evans³⁵ have published similar data concerning an additional series of 22 patients, for whom no other form of treatment was employed. Remission of hyperthyroidism was observed in a majority of cases of both series.

In the group of patients treated by Chapman and Evans,³⁵ the average dose of radiation given was two to three times as much as that used by Hertz and Roberts. In 20 of the 22 cases mentioned in Chapman and Evans' reports, hyperthyroidism was relieved and in 4 of the 20 cases myxedema developed. Mild reactions resembling radiation sickness occurred in six cases.

In all of the therapeutic trials just mentioned, the radioiodine employed was prepared in the cyclotron and consisted of a mixture of

about 90 per cent I^{130} and 10 per cent I^{131} . The chief therapeutic effect of this mixture has been considered to be due to the predominant short-lived isotope (I^{130}). Because of the physical limitations of the cyclotron this could be prepared in only small quantities and because of its short half-life, it was useful only to investigators in the immediate vicinity.

Since July 1946, pure I^{131} prepared in the chain-reacting uranium piles of the Clinton Laboratories at Oak Ridge, Tennessee, has been available in large quantities and consequently it is now receiving careful clinical trial. Since the physical characteristics of I^{131} are different from those of I^{130} , the effective dosage is certain to be different.

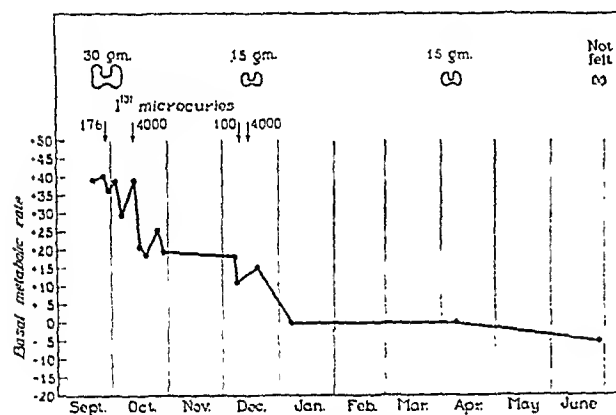


Figure 9. Treatment of recurrent exophthalmic goiter with radioiodine. The small doses of radioiodine initially given were tracers. The effect of the radiation on the size of the thyroid and the basal metabolic rate parallel the clinical improvement.

AT THE Mayo Clinic treatment with I^{131} is being tried in a selected group of cases of hyperthyroidism. The group is limited to elderly patients, those with serious complications which in themselves greatly increase the risk of thyroidectomy or which greatly reduce the patient's life expectancy, and patients whose exophthalmic goiters have recurred repeatedly after surgical treatment. The series of cases thus comprises a group in which the disease usually has been proved to be resistant to treatment.

Insufficient time has elapsed for evaluation of results following treatment with I^{131} for exophthalmic goiter. Remission has been induced in a majority of the patients treated and no serious untoward effects have thus far been observed (Figure 9). In a few instances myxedema has been produced. In a few others, persistence or recurrence of hyperthyroidism has been observed.

Treatment of malignant lesions of the thyroid—So far it appears that the possibilities of treating malignant lesions of the thyroid gland with radioiodine are very limited. The results of an early study of Hamilton, Soley and Eichorn³² indicate the reason for this. In a series of autoradiograms they observed that practically none of the iodine was deposited in malignant tissue; what radioiodine was collected in the thyroids of patients who had malignancy of the thyroid appeared in the normal thyroid tissue. However, Frantz and his co-workers³⁰ have reported a case in which thyroid carcinoma and distant metastatic lesions collected radioiodine in large amounts. Leiter and his associates³⁷ studied two additional cases. Both were instances of hyperfunctioning adenocarcinoma of the thyroid with hyperthyroidism, and in one, prolonged treatment with radioiodine effected remarkable arrest of widespread metastatic lesions in bones.³⁸

The studies of Marinelli and his associates³⁹ and of McArthur and Cope,³⁰ indicate that wide variations exist in the capacity of malignant lesions of the thyroid to collect radioiodine and considerable correlation exists between the type of tumor, the degree of differentiation, and the capacity to collect iodine. In general, the more adult the cell structure of a tumor, the greater the likelihood that significant quantities of radioiodine will be collected in it. Rawson estimated that roughly 15 per cent of thyroid tumors may be expected to collect radioiodine in some degree. It is unlikely that even this proportion will prove amenable to treatment with radioiodine.

For purposes of treatment it is not sufficient that a tumor collect merely detectable amounts

of radioiodine. For treatment to be possible, a tissue must collect radioiodine in sufficiently large concentration to produce radiation effects. From the data which are available, the proportion of tumors which meets this criterion is very small indeed. Treatment with radioiodine will be possible only in exceptional cases, unless some means can be found to increase markedly the avidity of thyroid tumor tissue for iodine. The studies of Leiter and his associates,³⁷ which Rawson and my associates and I²⁵ have confirmed offer some hope that total ablation of normal thyroid tissue and previous treatment with thiouracil may have this effect.

THE therapeutic application of radioiodine is complicated by the difficulties of determining the dose of radiation required. Various aspects of this highly technical subject have been discussed by Marinelli¹⁰ and by Chapman and Evans.³⁸ The biologic factors which must be known and measured in order to determine dosage include the actual weight of the thyroid gland, the quantity of a given dose collected in the thyroid and the rate at which the radioiodine is excreted subsequently from the thyroid. The purely physical factors include the qualitative characteristics and specific energy of the radiation of the isotope employed, as well as the half-life of the isotope. Most of the foregoing can be determined at least approximately, but there are probably still other variables which cannot. These include variations in radiosensitivity due to varying degrees of hyperplasia or the like. On this account it is likely that for the present at least dosimetry may remain on a rather empiric basis.

COMMENT

It requires constant re-emphasis that the use of radioiodine, either as a tool for investigation or as a therapeutic agent, is potentially dangerous. The handling of radioiodine requires the same kind of precautions against the insidious and disastrous consequences of radiation for the patient, the physician, and the technician as does the use of roentgen rays or radium.

This is particularly the case because of the penetrating character of the gamma rays. At present there is a serious dearth of accurate information regarding minimal quantities of radiation which are capable of producing radiation effects both in the thyroid gland and other organs. For the present, exploration of the field of usefulness of radioiodine remains a complicated undertaking which requires a skilled research team including internists, radiologists, biochemists, and physicists working in close collaboration.

No immediate side effects of an untoward character have been observed in patients given large quantities of radioiodine therapeutically. It will be necessary to wait many years before the same statement can be made regarding late effects. The quantities of radiation being employed in radioiodine therapy for hyperthyroidism are, by any standard of comparison with radium or roentgen rays, very large ones. One need only recall the history of radium or the roentgen rays to realize that the possibility of serious aftereffects of radiation, including malignant transformation, appearing years or even decades after exposure is a real one. The decision to treat nonmalignant disease with radioiodine must always be weighed against this unknown and possibly serious hazard.

SUMMARY

Radioiodine has proved to be a useful tool for the study of problems related to thyroid function both in animals and in human beings. It also has been used in the treatment of hyperthyroidism with some success but it is far too early to evaluate thoroughly the usefulness and limitations of this form of treatment. The possibilities of treating malignancy of the thyroid with radioiodine are very disappointing, since it appears probable that only in exceptional cases will this lesion prove amenable to such treatment. The use of radioiodine is hazardous because of the danger of radiation effects. The possibility of serious delayed effects of radiation requires careful consideration when radioiodine is employed for the treatment of nonmalignant disease.

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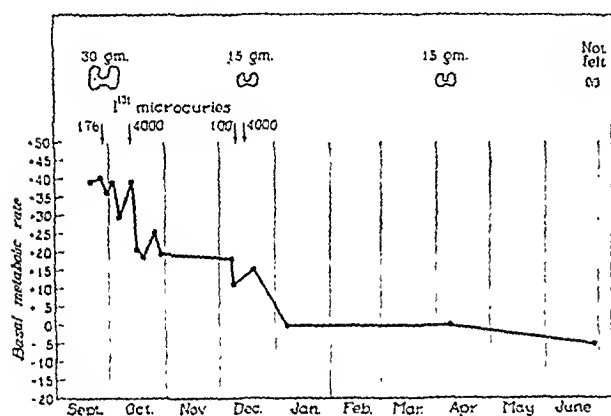


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Psychosomatic Gynecology

J. P. PRATT*

HENRY FORD HOSPITAL, DETROIT

A SERENE woman is a rarity. Serenity is the subconscious ambition of every woman. To achieve that goal she must have a tranquil mind. A tranquil mind is only to be had when mental and physical forces are coordinated. The physician is offered the opportunity to correlate the mental, emotional, environmental, and physical problems. How well he uses his opportunity depends upon his understanding, sympathy, and ability.

Treatment of mind and body—psychosomatic medicine—is not new. The development of various laboratory and technical procedures in the past hundred years has emphasized the importance of physical manifestations of disease. The influence of emotions on the bodily activities has been recognized since antiquity, but even today suitable measuring sticks for the emotions have not been devised. One cannot measure them with mathematical accuracy.

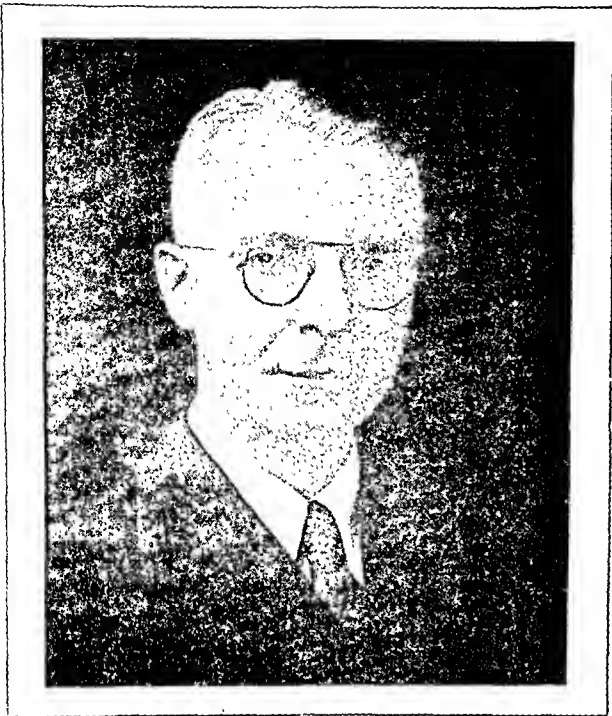
We are grateful to the psychiatrists for their recent trend towards simplification. Dr. C. C. Burlingame has said: "Most important of all, the psychiatrist must express himself in terms which can be understood by every medical practitioner, and psychiatry must be made an inte-

gral part of medicine. It does not take a great mind to make simple things complicated, but it takes a very great mind to make complicated things simple. Let psychiatrists, then, distinguish between psychiatric sense and psychiatric nonsense and bring simple hard-headed sense into the field, which contains the greatest public health problem of the world today."

More than one-half of all the hospital beds in this country are occupied by patients who are mentally ill. More than half of the symptoms and complaints of patients seen in the office or the home cannot be explained on an organic basis. The incidence of mental and emotional disorders is steadily rising. How shall the challenge of this large segment of illness be met? Briefly, the answer is, treat the patient as a whole. Combine common sense and simplicity with technical knowledge.

Compare the lives of two young women I saw a few years ago. Each of them had been born with the same deformity, extrophia of the bladder and a cloaca. One of them was an unwanted child in an unhappy home. Early in life she had been placed in an institution. No loving care came into her life. She was regimined with other unfortunate children, receiving merely food, shelter, and clothing. Through lack of education she was mentally retarded

*Surgeon-in-charge, Division of Obstetrics and Gynecology, Henry Ford Hospital, Detroit.



J. P. PRATT

and uncooperative. To all suggestions that something be done to improve her lot, she gave a flat refusal. No one would assume responsibility for her beyond providing the few simple necessities.

The other young woman was an only child, surrounded in her home by loving care and kindness. By a series of operations her ureters were transplanted, the defect of the bladder closed, and an artificial vagina made. During all those years her education was supervised so that she graduated from high school at 17 years. After that she was trained as a certified accountant. At the time I first saw her she was happily married and came to me to find out whether anything could be done to make it possible for her to become pregnant. Fortunately, she had a uterus and menstruated regularly. It was possible to give her hope which was important for her emotional stability. At the present time she is a happy wife hoping to be a mother. By contrasting the lives of the two women, the profound effect of environ-

ment is illustrated. One approaches serenity, whereas the other is far from it.

In many communities the general practitioner serves as obstetrician, pediatrician, and general family adviser. That position gives him a golden opportunity and a great responsibility, for it is generally believed that many of the neuroses developing in later life are based on experiences in childhood. The value of intelligent guidance of the parents is multiplied many times in the child because the child's early education must come from the parents, mostly the mother. Many of the feeding and nutritional problems of the child reflect the emotional stability of the mother, and little progress will be made without understanding her. It has been estimated that only about 50 per cent of mothers are fully maternal, while an almost equal number are classified as rejecting, oversolicitous, overprotective, overaffectionate, or dominating. Behavior problems in children can usually be traced to mothers of these types. When called to see the child, the physician may find that the mother should be the patient. Is he trained to recognize such a condition, to treat it, or to persuade her to see a trained psychiatrist?

WHEN a mother comes to the gynecologist she may find the real cause of her complaint far from her pelvic organs. A woman, 49 years of age, complained of leukorrhea. She had not menstruated for two years but had experienced only an occasional hot flush. No other symptoms that might be attributed to the menopause were recalled. Gynecologic examination revealed a normal reproductive tract with early involution. Examination of the scant vaginal secretion showed only epithelial cells and a few white blood cells.

To me, the pelvic examination was quite negative. She might have been dismissed by telling her that I found everything normal. Evidently something disturbed her or she would not have felt it necessary to consult a doctor. So many women fear cancer that in order to assure her I told her she had no cancer.

That made no impression for she had not even thought of that possibility. She appeared to be under nervous tension, but casual questioning revealed no obvious cause. Her husband was devoted to her. She was an excellent golfer and was active socially. I was puzzled and also intrigued. The problem was apparently not solved so she was given a return appointment in two weeks to give me an opportunity to get into her background.

At the next visit she complained of pain in her right lower quadrant and had lost 20 pounds. Again, examination revealed no obvious cause. Repeated visits after that for separate and varied complaints still revealed no obvious cause. However, she began losing her look of vitality and health and the glow of hope that the average, intelligent woman of middle age retains. Then one day I noticed in particular that in lowering herself into the office chair she let her weight rest on her wrists, an act which is definitely that of an old woman. She nervously clasped and unclasped her purse. This was so foreign to the woman of dignity and poise whom I used to know that my heart went out to her in sympathy, for I could see that she was deeply troubled. I managed to convey real sympathy to her and it broke down the barriers.

Concisely, her story was that her unmarried daughter was pregnant and about to have a child in a distant city. The daughter had confided in her mother only a few weeks before. Somehow she felt that she had failed her daughter because her daughter had not had enough confidence to tell her mother in the beginning. In reality the patient's symptoms were an expression of great emotional turmoil.

The corrective measure was to face the problem squarely. She told her husband of their daughter's plight, and then went to stay with the girl. The baby was born dead and the mother and daughter returned home. Their previously fine relationship was re-established. The problem was faced squarely, and although it was a sad experience, it broadened the woman and deepened her understanding, and she again regained her serenity. This woman was

on the way to becoming a chronic invalid. What an opportunity would have been missed if, on the first occasion, she had been dismissed as normal.

The behavior of the mother in the instance just cited implies a feeling of guilt. She thought she had been a good mother, always glad to share her daughter's joys and sorrows. How had she failed so that the daughter had not told her earlier of her great trouble? The daughter dearly loved her mother and hoped that luck or good fortune would provide an "out." As the months passed, the pregnancy became more obvious. By accident the mother learned of the daughter's pregnancy while the daughter was on a supposed visit in a distant city. The mother had not failed. There was no guilt on her part, though she was difficult to convince. When the feeling of guilt was finally overcome, tranquillity was not yet achieved. Many perplexing indecisions had arisen. Could she or should she tell her husband? What should be done with the baby? What story could she tell her friends to explain her absence from the city while with her daughter? The problems were faced squarely, and one by one the indecisions were relieved.

THE INCREASING tempo of cancer education has aroused the public. A normal response to the warning should take the individual promptly to her physician for examination. If she is told that she has cancer, she accepts the advice given and follows the prescribed treatment. If she is told that she does not have cancer, the subject is gratefully dismissed. Another group fear that they may have cancer and fear to be told the truth, thinking that their plight would be hopeless. They put off going to the physician for weeks and months. The longer they delay, the more their anxiety increases. The fear may be so intense that nothing will induce them to go to the doctor for any complaint. Another group would like to know whether they have cancer, but they fear to hear the terrifying word. They present all sorts of complaints as an excuse for examination. No

physical basis for their complaint is found. This presents an excellent opportunity to the physician to assure them that nothing wrong has been found and to add, "You may be sure that you do not have cancer." It is helpful in reporting the results of examination to try to anticipate to which group the patient belongs. Rarely should they be dismissed with the mere statement, "Nothing is wrong with you."

A surprising number of women fear insecurity. This manifests itself in a variety of ways. One of these is a spurious backache. A very striking example of this is a woman who came to me through the orthopedic department, where they found nothing wrong with her. An attractive woman of 31, she was well groomed and well dressed, and wore a magnificent mink coat and beautiful jewels. Nevertheless, this outward manifestation of well-being belied her inner self. She seemed listless and disinterested. Because of her indifference it was difficult to get a satisfactory history. She merely persisted in saying that she had a backache. Examination showed her pelvic organs to be normal. Finally, conversation revealed that the beginning of her backache was coincident with the finding of a note from another woman to her husband. This incident broke an otherwise tranquil existence. Further investigation her revealed that her husband was persistently consorting with other women. When confronted with the facts, the husband admitted, then flaunted his infidelities. This was a threat to her security. Hence, her apprehension and nervous tension resolved itself into a fictitious backache.

The problem was now before us. What would be the solution? On her next visit her appearance was more hopeless and woebegone than before. My first sentence to her was, "Mrs. —, you are a very attractive woman. Why don't you show some spirit and do something about your problem?" She immediately became interested. I pointed out the real reason for her backache and explained that the cure lay within herself. She left the office determined to do something about it.

Six months later she returned exuberant,

happy, and full of the joy of living. One seldom sees such a complete metamorphosis in so short a time. She told me that on her way home from the office after her previous visit she went directly to a school of modeling and registered. She went through a rigid course during which she regained confidence in herself and found that she could earn her own living. Her husband soon found that he had an interesting, attractive, and sought-after wife, beside whom his inamoratas paled. He again courted her. The backaches vanished. She was again a serene woman. Recently I saw her pictured in a national ad.

THE ILLUSTRATIONS cited briefly were selected as examples of individuals who were, fundamentally, emotionally stable but were brought to the crossroads by a crisis. If misdirected, they might have become confirmed hypochondriacs or even worse. Such problems are not psychiatric at the onset, but if allowed to go unrecognized might well become serious, and in the meantime, irreparable damage would have been done. In the beginning such problems lie within the reach of any physician who has imagination, understanding, and sympathy. Solution of a problem of this kind not only is a great benefit to the patient but also adds interest to the life of a physician.

Notable advances in science have made it possible to diagnose, heal, and prevent disease. Philosophers were long concerned with analyzing the mind apart from the body. In recent years we have come to appreciate the significance of the close relationship of body and mind, and we are learning more and more that emotions affect the body and the body affects the emotions. This is psychosomatic medicine.

The physician has a responsibility and an opportunity. A responsibility because the patient has come to him with the hope of being helped. He has an opportunity to remake a life.

By elimination of problems, fears, anxieties, and indecisions, most women can be helped to that serenity of spirit that is symbolic of a happy woman.

Carcinoma of the Lung

ALTON OCHSNER,¹ MICHAEL DeBAKEY,² AND LEONARD DIXON*

SCHOOL OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA AND THE
OCHSNER CLINIC, NEW ORLEANS

PRIMARY cancer of the lung was considered a relatively rare and hopeless disease until about fourteen years ago. Since that time both of these concepts have been refuted, and the condition has developed increasing importance.

INCIDENCE

Although some variations exist on the absolute incidence of carcinoma of the lung, there is almost complete agreement among investigators in all parts of the world that the disease is increasing in incidence and now ranks high as a primary form of cancer, comprising about 5 per cent of all malignancies. The increasing frequency in this country is shown by Dorn's studies on the incidence of the disease. This observer found that between 1914 and 1930 the death rate from cancer of the lung increased 3.7 times, although during this same period there

was an increase of only 20 per cent for all forms of cancer combined. The death rate continued to increase during the period from 1930 to 1940. Similar observations have also been made at various institutions. This is exemplified by our own experience. Thus, at the Charity Hospital in New Orleans during the ten-year period ending December 1946, there was a steady rise in the incidence of carcinoma of the lung, whereas incidence of carcinoma of the stomach for the same ten-year period showed, if anything, a slight decrease. Whether this increase in the incidence of carcinoma of the lung is real or apparent is open to speculation. The important fact remains, however, that the disease has now increased to the point where, at least in the male sex, it must be regarded as a relatively common form of malignancy.

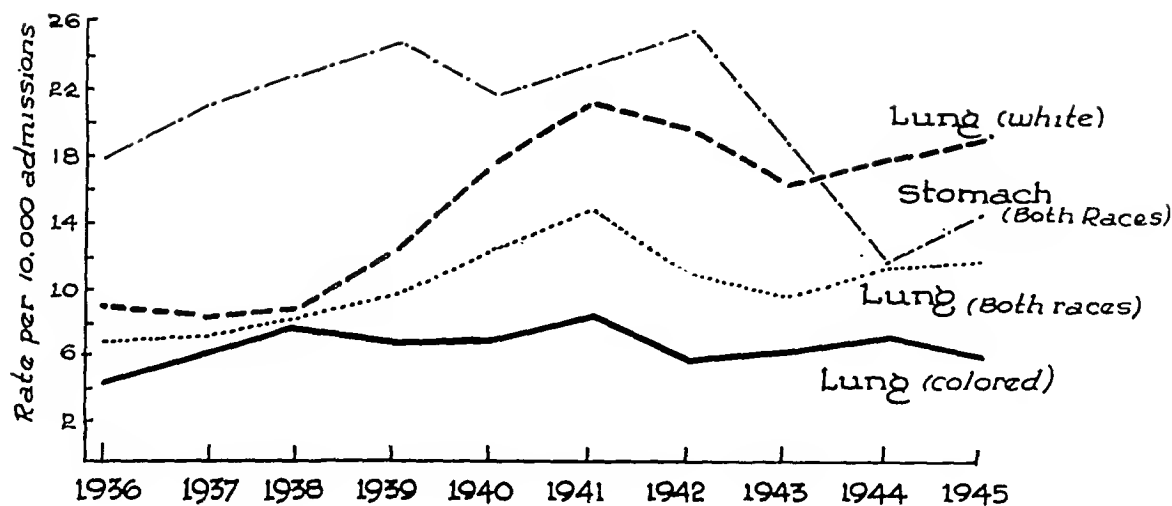
The disease seems to occur most frequently in elderly males. The highest incidence is found in the sixth decade, and more than 85 per cent of the cases occur in the fifth to the seventh decades. The male sex predominates in a ratio of about 5 or 6 to 1. A study of the racial incidence at the Charity Hospital in New Orleans, where among total admissions the white and colored races are found in equal proportions, shows that in cancer of the lung the white race predominates in a ratio of about 2 to 1. Various

¹William Henderson Professor of Surgery, School of Medicine, Tulane University, and Director of Section on General Surgery, Ochsner Clinic, New Orleans.

²Associate Professor of Surgery, School of Medicine, Tulane University of Louisiana, New Orleans.

*From the Department of Surgery, School of Medicine, Tulane University of Louisiana, and the Ochsner Clinic, New Orleans, Louisiana.

Presented before the meeting of the Interstate Postgraduate Medical Association of North America, St. Louis, Missouri, October 14 to 17, 1947.

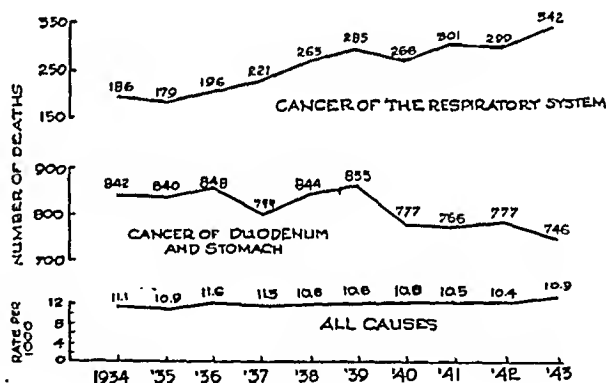


Incidence of Carcinoma of Lung and Stomach Based Upon Admissions at Charity Hospital January 1, 1936 to January 1, 1946

etiologic factors have been considered as possibly contributing to the development of the disease, including occupation, smoking, inhalation of irritating dusts and fumes, and previous pulmonary infections. An analysis of our cases from this standpoint failed to reveal any factor having special significance.

PATHOLOGY

Most primary malignancies of the lung are bronchiogenic in origin. Alveolar carcinomas occur only rarely, and primary sarcomatous forms are also infrequent. In our series of 489 cases, all but 6 were considered bronchiogenic in origin. These 6 cases included 2 cases each of fibrosarcoma and lymphoblastoma and 1 case each of melanosarcoma and neurogenic sarcoma. The right lung is involved somewhat more frequently than the left. In a previously collected series of 4,732 cases, 58.3 per cent involved the right lung and 41.6 per cent the left lung. In our personal series of 176 cases in which resection was done, 103 (58.5 per cent) involved the right side and 73 (41.5 per cent) involved the left side. The two upper lobes and the right lower lobe were involved with approximate



Mortality—State of Missouri

equal frequency, i.e., 24 per cent. The left lower lobe was involved in 12.5 per cent.

CLINICAL MANIFESTATIONS

As has been emphasized previously, the clinical picture of carcinoma of the lung is not distinctly characteristic, especially in its earlier stages. This fact, in addition to the usually insidious onset, undoubtedly accounts for the frequent delay in diagnosis. Among the commonest



ALTON OCHSNER



MICHAEL DeBAKEY

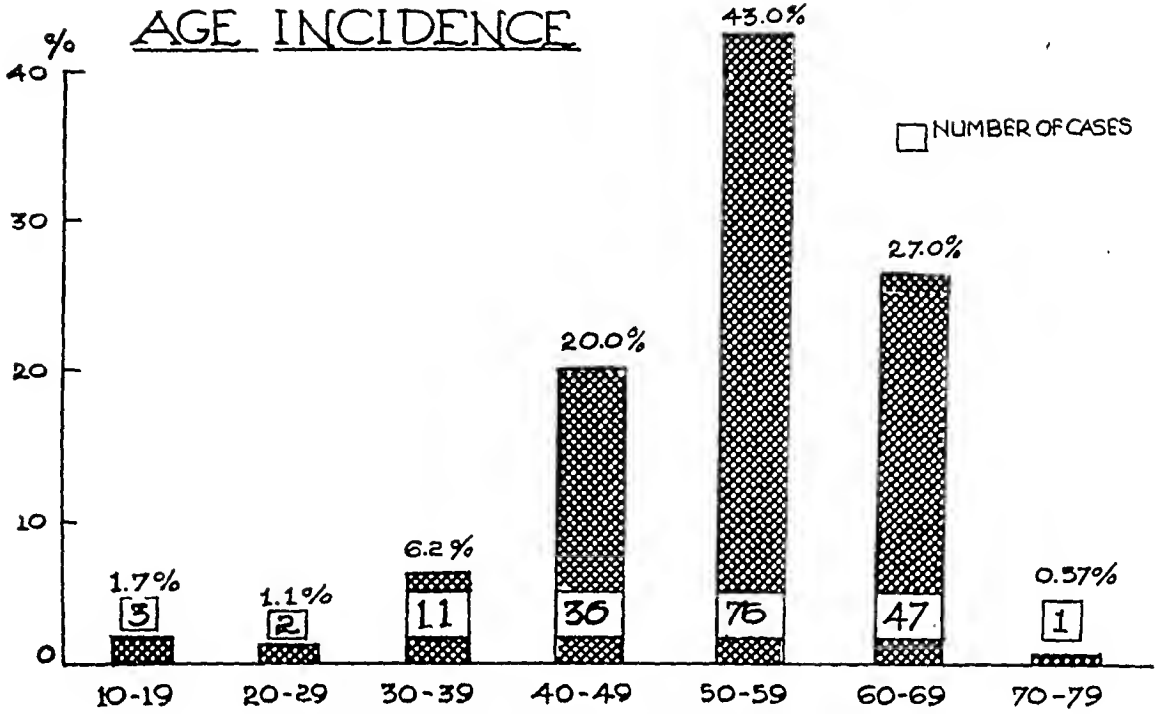


LEONARD DIXON

manifestations that are encountered, in order of their frequency, are cough, loss of weight, discomfort or pain in chest, hemoptysis, previous respiratory infection, and dyspnea. Cough, which is by far the most common complaint and often the earliest in development, is unfortunately too easily attributed to smoking. This is readily understandable since the majority of the adult population smoke and since it is often the actual cause of the complaint. Nonetheless, it is important to bear in mind that the cough may not be due to smoking but to an early developing lung cancer, particularly in elderly males and especially if the cough persists, shows any change in character, or becomes associated with other thoracic symptoms. Of considerable significance also is the history of a previous respiratory infection from which the patient recovers slowly or incompletely. The full significance of this series of events is often not appreciated until several months have elapsed and the disease has advanced considerably. The frequency with which this occurs emphasizes the need for greater awareness of the possibility of carcinoma of the lung as the cause for such manifestations. On the basis of our experience we have become convinced that the key to improvement in the early diagnosis of lung cancer lies in the wider

recognition and the constant recollection that symptoms referable to the respiratory system, no matter how vague or insignificant they may appear, in patients over 40 years of age and especially in males, may be caused by pulmonary malignancy.

PHYSICAL findings in carcinoma of the lung, like the symptoms, are variable and often indefinite, especially in the early stages, when examination, as a rule, reveals nothing characteristic or even significant. The character of the findings depends to a great extent upon the site, size, and location of the tumor. In general, tumors which encroach and tend to obstruct the larger bronchi produce more discernible physical findings than tumors involving the more peripheral areas of the lung. Thus a relatively small tumor that completely occludes a main stem bronchus can produce, as a consequence of the extensive atelectasis thus caused, striking physical findings, whereas a peripherally located tumor may grow to considerable size before it produces readily apparent physical findings. Experience with this disease has emphasized the unreliability of ordinary physical examination as a means of detecting carcinoma of the lung in its early stages.

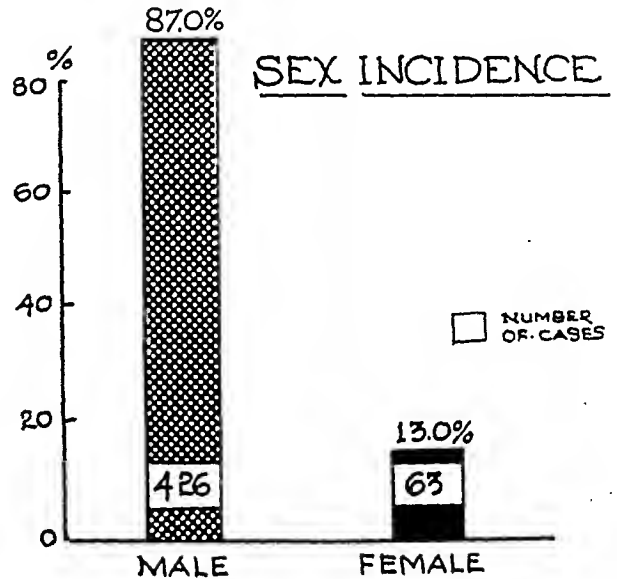


176 Cases Pulmonary Malignancy Treated by Resection

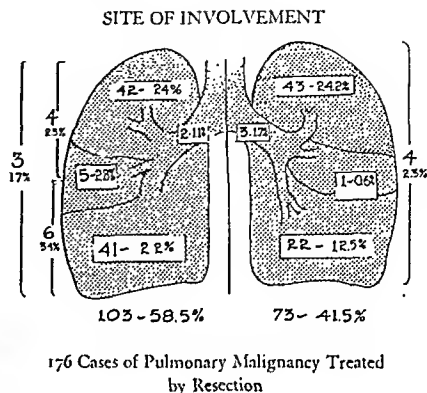
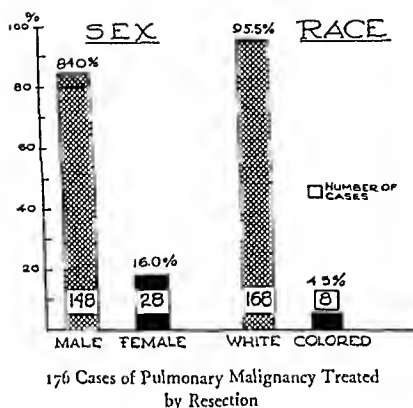
DIAGNOSIS

The diagnosis of carcinoma of the lung is usually not difficult once the condition is suspected; suspicion of its presence should always be aroused in any patient, and especially in a male over 40 years of age, who has a persistent cough, unexplained thoracic discomfort, or hemoptysis. Indeed, consideration of its possible presence is the most important factor in the diagnosis of lung cancer.

The most useful diagnostic methods are roentgenography, bronchoscopy, and cytologic examination of the sputum or bronchial secretions. Roentgenography is of particular value and will provide suggestive evidence of the lesion in a high proportion of cases; in our experience it has provided such information in over 85 per cent of the cases. Serial roentgenograms are especially useful in early lesions, for by this means it is possible to detect the progressive development of even small growths.



489 Cases of Pulmonary Malignancy



They are also helpful in distinguishing hilar shadows produced by a centrally located lesion and those caused by normal structures.

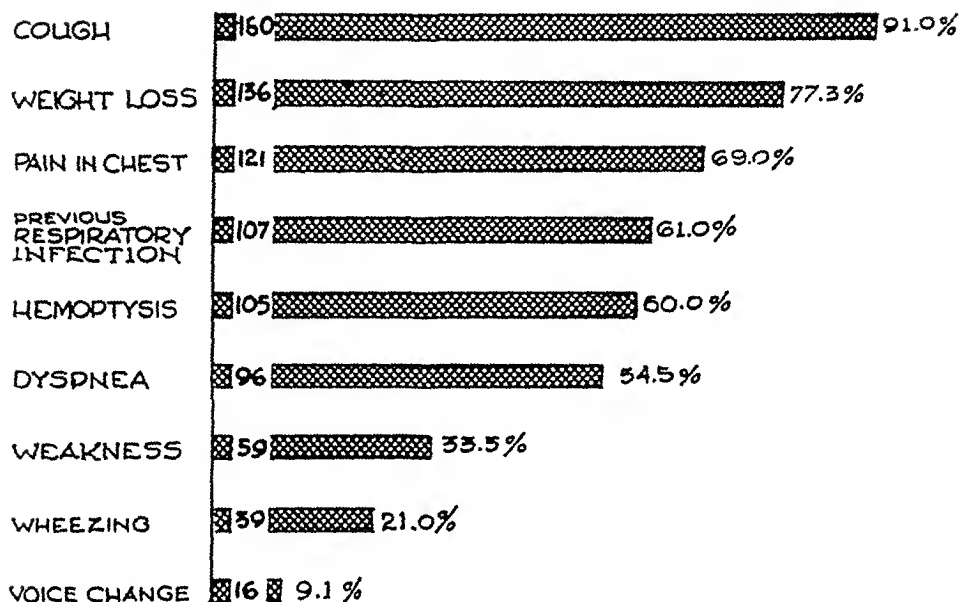
The character of the roentgenogram in lung cancer varies considerably and depends upon the site, size, and type of growth of the tumor. A large opaque shadow can be produced by a relatively small lesion if it occludes a large bronchus. In such a case the opacity largely reflects the extent of the consequent atelectasis. In other instances the picture is suggestive of a lung abscess. This is due to the stasis produced in an area of the lung drained by a bronchus which is occluded by the tumor or as a consequence of interference with the blood supply in the center of a rapidly growing tumor resulting in necrosis and infection. In fact, the demonstration of an abscess in a man over 40 years old that cannot be satisfactorily explained should always arouse suspicion of an underlying malignancy.

Routine roentgenologic studies of the chest should be used more frequently in the clinical examination of patients, especially in the older age groups. The value of this procedure is shown by the fact that it permitted the discovery of the growth, previously unsuspected, in 7 of

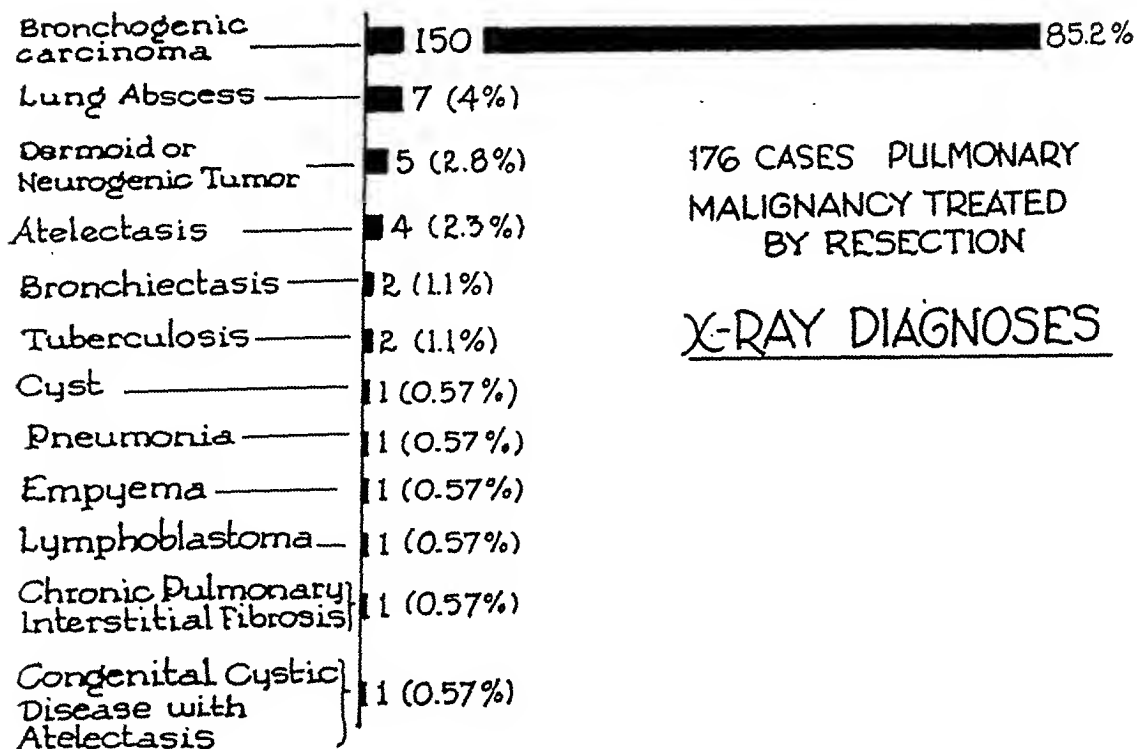
the 176 cases in our resected series. In 2 other cases the tumor was discovered by roentgenograms made for fractured ribs.

In certain cases bronchoscopy is perhaps the most accurate method of diagnosis because it permits visualization and biopsy of the lesion. The procedure is of little diagnostic value, however, in lesions located in the periphery of the lung or in the upper lobes since they are beyond the vision of the bronchoscopist. Unfortunately, these constitute a large proportion of the cases. It will be recalled that somewhat less than half the cases are situated in the upper lobes. Even though some of these tumors may be visualized when located near the opening of the upper lobe bronchi, it is usually not possible to obtain a biopsy in such cases. In our 176 cases in which resection was done, bronchoscopic examination was performed in 150, and of this number a biopsy with a positive histologic examination was done in 71 cases, or 41 per cent, of the entire group. This figure is lower than that frequently reported but may be explained by the fact that exploration was done in a large number of our cases in which a positive preoperative diagnosis

COMPARATIVE INCIDENCE OF RECORDED SYMPTOMS



176 Cases of Pulmonary Malignancy Treated by Resection

176 CASES PULMONARY
MALIGNANCY TREATED
BY RESECTIONX-RAY DIAGNOSES

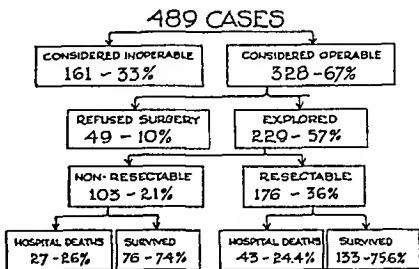
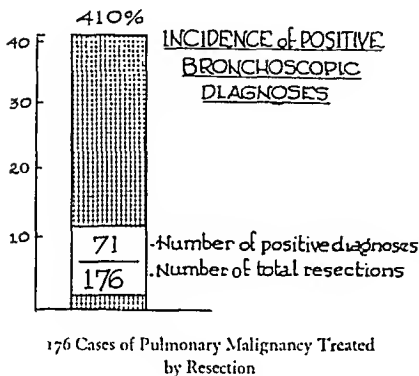
could not be established. The fact that the lesion was in the upper lobes in almost half of our resected cases supports this explanation.

Cytologic examination of the sputum or bronchial secretions is still another valuable diagnostic procedure. With increasing experience, this may prove to be the most useful of all diagnostic methods and would seem to have particular value in cases in which the tumor is beyond the range of bronchoscopic visualization. Similar examination of aspirated pleural fluid may also be made, though the demonstration of tumor cells in such cases is usually indicative of a hopeless prognosis.

In a certain proportion of cases a positive diagnosis cannot be established except by exploratory operation. This occurred in two-thirds of our 489 cases. On the basis of our experience we are convinced that in cases in which there is good suggestive evidence of lung cancer but in which the diagnosis cannot be established preoperatively despite thorough studies, exploratory operation is justified. The operative risk from exploration is now minimal, and it frequently reveals an early and, therefore, operable growth.

TREATMENT

The only curative treatment for cancer of the lung is surgical extirpation of the tumor-bearing



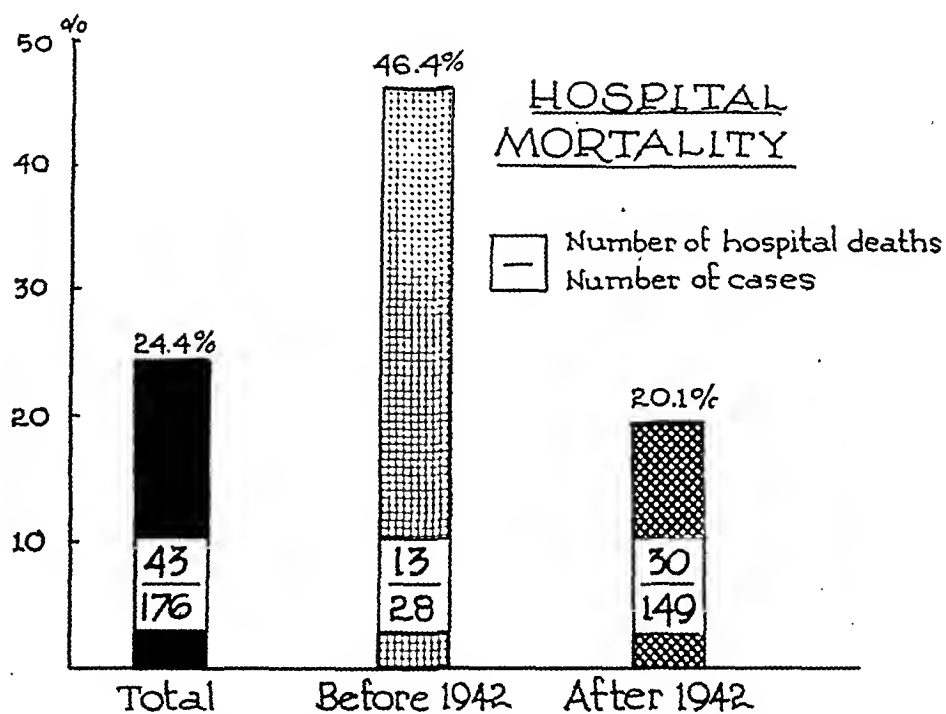
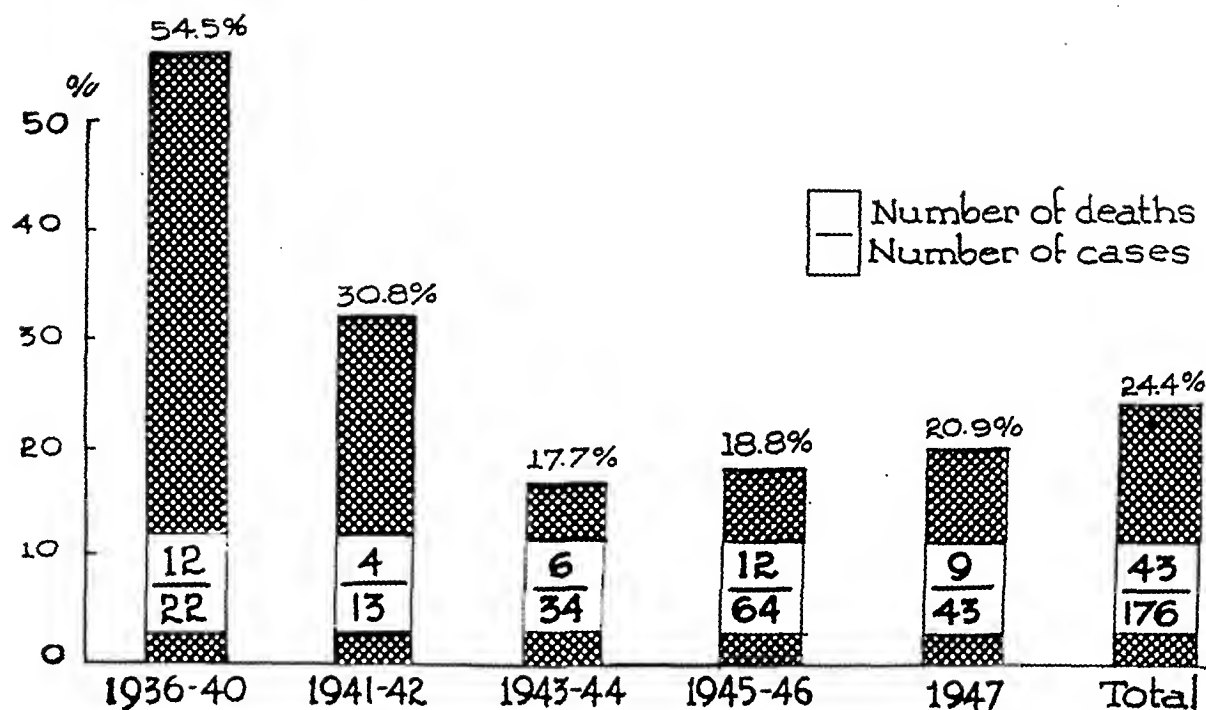
Results in 489 Cases of Pulmonary Malignancy
Diagnosed Clinically

ing lung and regional lymph nodes. All other forms of therapy, including irradiation and methyl-bis, are of palliative value only and should be reserved for inoperable cases. With few exceptions pneumonectomy is considered the procedure of choice because it permits more thorough extirpation of the involved tissue and potentially involved hilar lymph nodes. With increasing experience, we have come to believe there are relatively few contraindications to exploration. At present our indications of definite inoperability are the demonstration of distant metastases, obvious involvement of the carina or trachea, and the observation of malignant cells in the aspirated pleural fluid. All other cases should be given the advantage of exploration because it is the only means by which a definite decision concerning resectability of the lesion can be made.

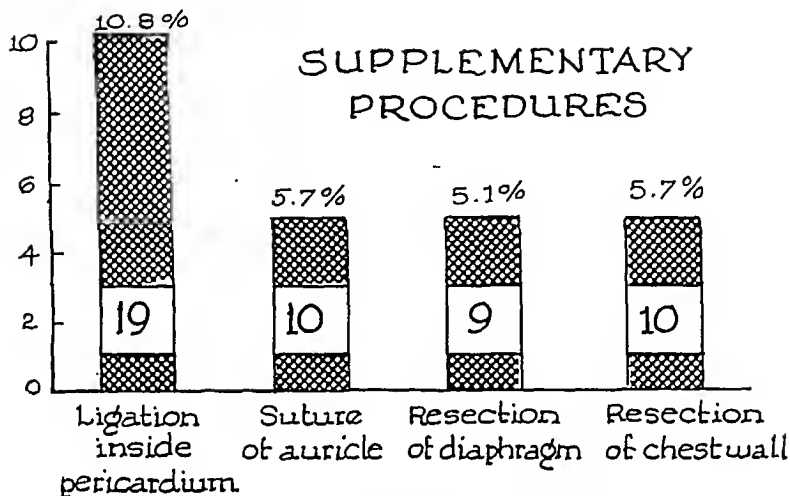
ANALYSIS OF RESULTS

Our experience with primary pulmonary malignancy is based upon a total of 489 cases. Of this number 161 (33 per cent) were considered clearly inoperable at the outset. Of the remainder, which were considered operable, 49 refused surgery and 279 (57 per cent) were explored. Of the 279 cases explored, 103 were nonresectable, and 176, or 36 per cent of the entire group, were resected. Thus, of every 3 patients with carcinoma of the lung, 1 will appear

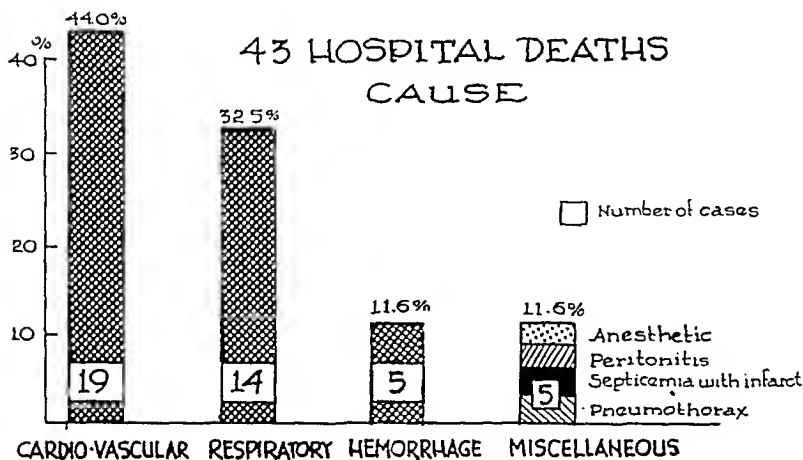
HOSPITAL MORTALITY IN 176 CASES



176 Cases of Pulmonary Malignancy Treated by Resection

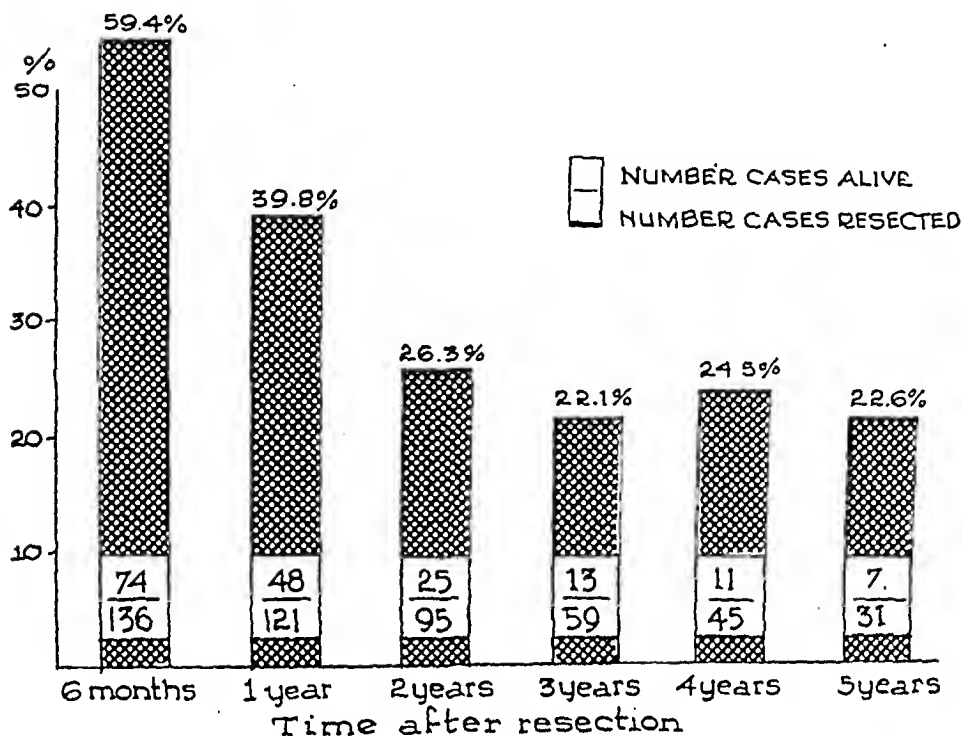


176 Cases of Pulmonary Malignancy Treated by Resection



176 Cases of Pulmonary Malignancy Treated by Resection

Survival Rate in Primary Pulmonary Malignancy After Resection



inoperable at the outset, and of the remaining 2 cases subjected to exploration, only 1 will prove resectable. These operability figures are somewhat higher than most of those recorded in the literature, but they are still much too low, a fact which emphasizes the need for earlier diagnosis.

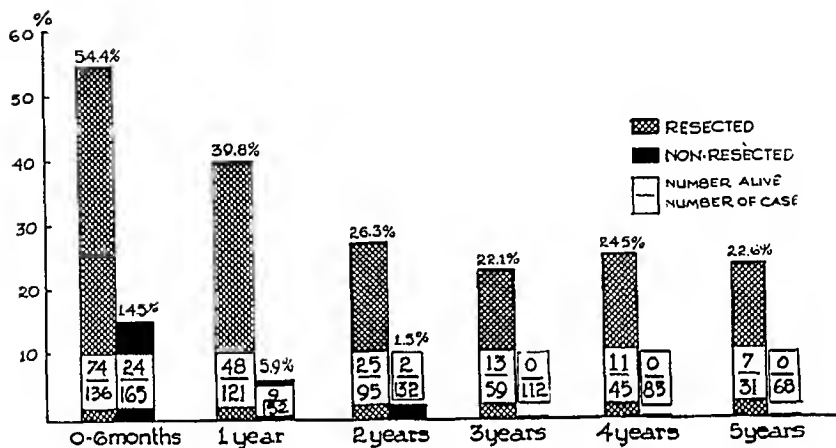
OF THE 176 patients in whom resection was performed, 43 died in the hospital, giving a total hospital mortality of 24.4 per cent. With increasing experience and with improvement in the pre- and postoperative care of these patients, there has been a fairly steady decrease in the immediate operative mortality. This is shown by the mortality for the periods before and after 1942, the respective figures being 46 per cent and 18 per cent. Although there has been a steady reduction in the operative mor-

talidity, it is doubtful from an analysis of the causes of death that it will be reduced either much more or much below 10 per cent. Among the causes of death immediately following operation cardiovascular lesions were by far the most frequent, accounting for approximately half the cases. In many patients in this age group with cancer of the lung, cardiovascular disturbances are likely to be present, frequently in association with other constitutional diseases. As pointed out previously, they represent a risk which must be assumed in pneumonectomy for this condition, unless the criteria of operability are so strictly limited that patients in whom they may occur are excluded from surgery and are thus denied their only chance of life.

Follow-up studies have been made on every patient in our series in which resection was done, and the survival rate over a five-year

PULMONARY MALIGNANCY

Comparison of Survival Rates Among Resected and Non-resected Cases



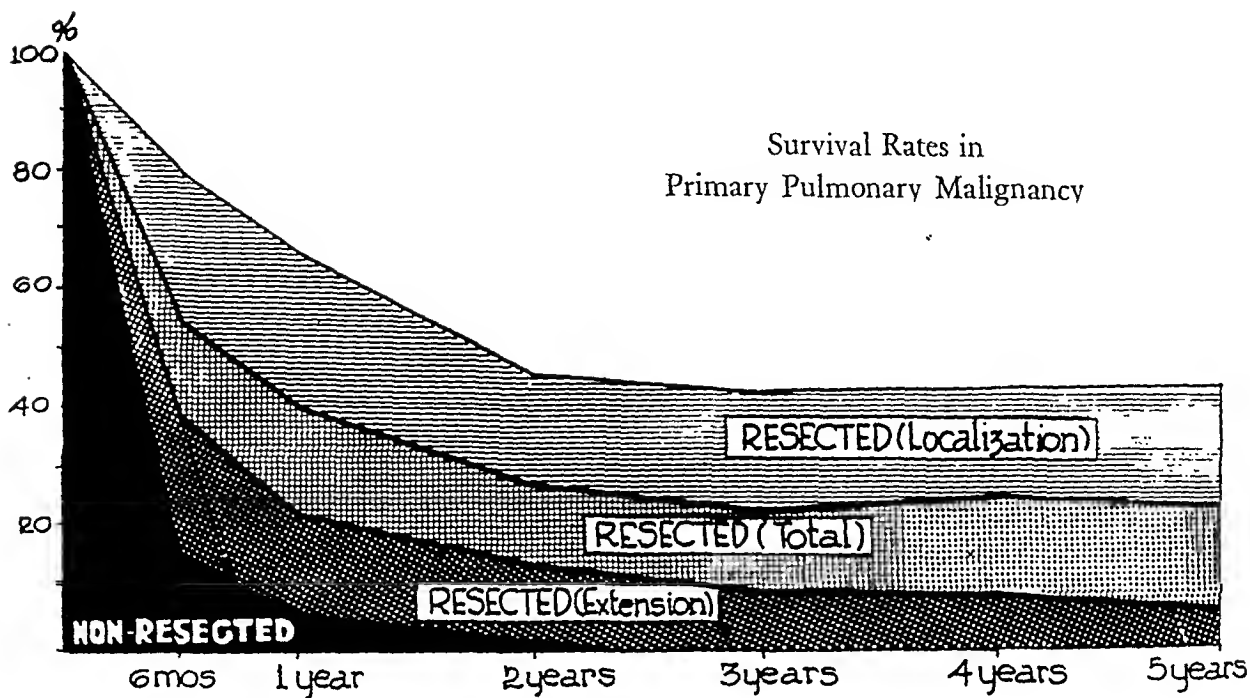
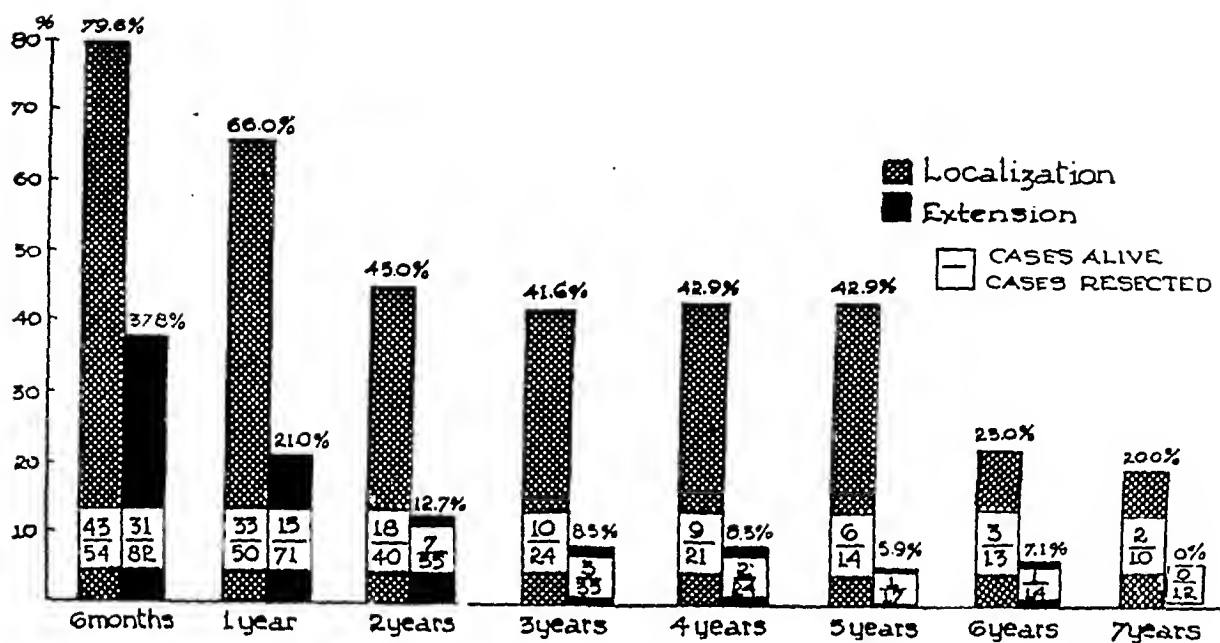
period has been calculated from these data. The results of this analysis show that a little more than half (54.4 per cent) the patients survive the first six months, approximately 40 per cent the first year, 26 per cent the second year, and almost 23 per cent live five years or longer. Thus, it will be observed that the distribution curve for the survival rate drops rather rapidly within the first year after pneumonectomy for carcinoma of the lung, but by the second year it begins to be stabilized and continues almost as a plateau until the fifth year. It would appear that a patient who lives through the second year after operation has an excellent chance of being alive at the end of the fifth year.

A comparison of these survival rate figures for the resectable cases with those obtained for the nonresectable cases provides some idea of value of the surgical treatment in carcinoma of the lung. The survival rate figures for the non-resectable cases were found to be as follows: approximately 15 per cent for the first six months,

6 per cent for the first year, 1.5 per cent for the two-year period, and none for three years or more. Thus over 95 per cent of the patients with nonresectable lesions died within the first year after the diagnosis was established, and no patient lived three years or more.

Analysis of these data was done in a number of different ways in order to determine the influence of various factors upon the survival rate. It was found that the most significant factor was the status of the growth, i.e., whether or not it had extended beyond the borders of the lung at the time of operation. Thus, the five-year survival rate for patients with a lesion still confined to the lung was 43 per cent, whereas for those in whom the lesion had extended beyond the borders of the lung this rate was 6 per cent. Here again the figures emphasize the need for earlier diagnosis; the striking difference between 6 per cent and 43 per cent represents the difference between the later, more advanced process and the early localized lesion.

Survival Rates in Pulmonary Malignancies After Resection According to Extension and Localization of Lesion



CARCINOMA OF THE STOMACH



CARCINOMA OF THE LUNG



As emphasized previously, the survival rate for carcinoma of the lung is as high as, if not higher than, that for carcinoma of the stomach; yet the latter condition has received more attention from the profession for a longer period of time. On this basis it seems reasonable to be-

lieve that with greater awareness of the problem of pulmonary malignancy, and consequent increase in the proportion of cases that are diagnosed early, there should be considerable improvement in the survival rates of the disease.

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CLINICAL DIAGNOSIS BY LABORATORY METHODS, by James Campbell Todd, M.D., Late Professor of Clinical Pathology, University of Colorado School of Medicine; Arthur Hawley Sanford, M.D., Professor of Clinical Pathology, Mayo Foundation, University of Minnesota; with the collaboration of George Giles Stilwell, M.D., Division of Clinical Laboratories, Mayo Clinic. 11th Edition. 954 pages, with 397 figures. Philadelphia and London: W. B. Saunders Company, 1948. Price \$7.50.

THE ACUTE BACTERIAL DISEASES—Their Diagnosis and Treatment, by Harry F. Dowling, M.D., Clinical Professor of Medicine, George Washington University; with the collaboration of Lewis K. Sweet, M.D., Chief Medical Officer in Pediatrics and Infectious Diseases, Gallinger Municipal Hospital, Adjunct Clinical Professor of Pediatrics, George Washington and Georgetown Universities; and Harold L. Hirsh, M.D., Assistant Professor of

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Diagnosis and Treatment of the Anemias

CYRUS C. STURGIS*

UNIVERSITY OF MICHIGAN MEDICAL SCHOOL, ANN ARBOR

MY TOPIC today is a discussion of the diagnosis of various types of anemia. I would also like to make a few general remarks concerning the etiology and treatment of these conditions.

An anemia may be defined as a reduction in the hemoglobin of the blood below the normally accepted values. Our own conclusions at the University of Michigan, after an extensive study of many normal persons, is as follows: (1) If 100 per cent is accepted as 15.6 gm. of hemoglobin per 100 cc. of blood, the lower limit of normal for adult males is 13.0 gm. or 83 per cent, and for females it is 12.0 gm. or 77 per cent; (2) ordinarily patients do not experience the usual symptoms of an anemia unless the hemoglobin falls to the vicinity of about 11 gm. or 70 per cent, or lower; (3) the physiologic anemia of pregnancy, due entirely to dilution of the circulating blood, may lower the hemoglobin of a pregnant woman to 64 per cent under normal conditions. Hence a true anemia of pregnancy is not present unless the hemoglobin is below this figure.

*Professor of Internal Medicine, Director of Simpson Memorial Institute and Chairman of the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor.

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FREQUENCY OF ANEMIA

Anemia is one of the most frequently encountered abnormal conditions in the practice of medicine. Regardless of whether one is engaged in general practice or in any one of the numerous specialties of medicine, patients with such a disorder, of one type or another, will be observed each day. Somewhere between 12 and 20 per cent of all patients admitted to a general hospital in the United States will have a clinically significant reduction in hemoglobin. One of every 8 (12 per cent) of the patients admitted to the inpatient and outpatient departments of the University of Michigan Hospital have such a condition. Over one-half of all pregnant women observed consecutively in our maternity outpatient department some years ago had a pathologic anemia, some severe. In a prosperous farming district near Ann Arbor, Michigan, a survey made over a period of a year showed that about 30 per cent of all pregnant women had an anemia more severe than the physiologic anemia of pregnancy. Studies made some years ago in England indicated that one of every two of the women and children of certain economic classes had a hemoglobin of the circulating blood which was below normal standards.

There are two points which I wish especial-



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ly to emphasize in regard to the anemias. One is that they are commonly encountered in the practice of medicine. Figures to substantiate this statement have already been given. The other is that in a large percentage, the variety of anemia can be determined easily and the condition controlled by simple and inexpensive measures.

ANEMIA DUE TO INFECTION

In a study of patients with anemia at the University of Michigan Hospital, it was found that 41 per cent had a normocytic, normochromic anemia with a mild decrease in the hemoglobin and red blood cell count. The former was often in the vicinity of 60 per cent and the latter about 3,000,000 per cubic millimeter. This variety is due to any type of chronic infection which produces an anemia in some obscure manner by interference with the normal synthesis of hemoglobin. Such an infection may be in the urinary tract, pelvis, bone,

respiratory system, or elsewhere. It is the type of anemia seen in chronic rheumatoid arthritis and also in acute rheumatic fever. Treatment of such anemia consists in: (1) the elimination, if possible, of the infection either by surgical means, with or without the use of sulfonamide drugs, penicillin, or streptomycin, and (2) use of blood transfusions, provided the anemia is of such an extent that their use is warranted. Iron, liver, desiccated stomach, folic acid, and other antianemic measures which are so effective in other types of anemia are of no value.

IRON DEFICIENCY ANEMIAS

PROBABLY the most important anemia is that due to iron deficiency. This is because it is almost as common as anemia due to infection (it has an incidence of 39 per cent of all our patients with anemia), and it is almost always controlled effectively by means of iron, which is an easily administered and inexpensive remedy. Iron deficiency anemias are most commonly associated with chronic hemorrhage. In the male this is most frequently due to bleeding from the gastrointestinal tract. This bleeding may occur in the form of epistaxis; may arise from esophageal varices in association with cirrhosis of the liver; cancer of the stomach or the large bowel, the sigmoid, or the rectum; peptic ulcer; chronic ulcerative colitis; or hemorrhoids. It is the constant daily loss of small quantities of blood, often unrecognized by the patient, that is of greatest importance from this standpoint.

In the female, the most common cause of chronic hemorrhage is the loss of excessive quantities of blood as a result of vaginal bleeding, although chronic gastrointestinal bleeding is also important. Studies have shown that a woman may lose two or three times the normal amount of blood at the menstrual periods and not be aware that abnormal bleeding is present. When this occurs for many months, a chronic anemia results from this cause alone, although the patient may assert positively that there has been no excessive loss of blood.

OTHER causes which may contribute to an iron deficiency anemia are as follows: (1) rapid growth in infancy and childhood, (2) infection, (3) achlorhydria, (4) a diet low in iron, and (5) rapidly repeated pregnancies. It is unlikely that any one of these causes is responsible for the development of an anemia when acting alone, but the effect of two or more may produce a clinically significant lowering of the hemoglobin. On the other hand, a chronic hemorrhage without other associated causes may be solely responsible for an anemia of varying degree, depending on the amount of blood lost. Also, although chronic hemorrhage may be the main cause of blood loss, the anemia may be intensified by the action of the other factors mentioned.

DIAGNOSIS OF IRON DEFICIENCY ANEMIA

How may an iron deficiency anemia be recognized? In the first place it should be kept in mind that such an anemia is one of the most common types encountered, especially in women and children. Second, there may be an apparent history of bleeding, and finally, the condition has a distinctive and easily recognized blood picture.

This type of anemia is a hypochromic, microcytic variety which is usually characterized by a moderate reduction in the red blood cell count to the vicinity of 2,500,000 to 3,000,000 per cubic millimeter, associated with a more pronounced decrease in hemoglobin, often to about 25 to 30 per cent. The most important characteristic is a low color index. For example, when a color index of 0.5 is present, it can almost always be deduced that an iron deficiency anemia, usually one due to chronic hemorrhage, is present. The only exception to this statement is that an anemia with such a low color index may be associated with Cooley's or Mediterranean anemia, a disorder rarely encountered in this part of the world. This also is the only type of anemia with a low color index which does not respond to administration of iron. If the hematocrit reading is determined and the mean corpuscular volume and corpus-

cular hemoglobin concentration calculated, the former will be in the vicinity of 60 to 70 cubic microns (normal from 86 to 96 cubic microns) and the latter from 25 to 28 per cent (normal 29 to 31 per cent).

TREATMENT OF IRON DEFICIENCY ANEMIAS

Treatment of such anemias is exceedingly simple and results attained are usually excellent. The success of such therapy depends on adherence to the principle of administering an adequate amount of iron orally to a patient in whom the diagnosis of an iron deficiency anemia is certain. It should be emphasized that entirely satisfactory results follow the administration of the proper dosage of iron alone. When, for example, iron in the form of ferrous sulfate 0.3 gm. (5 gr.) is given three times daily after meals, definite evidence of improvement should be present within two weeks. If this does not occur, the dose should be increased to 0.6 gm. (10 gr.) three times daily after meals, for an additional two weeks. If improvement still does not follow, it should be concluded that either the diagnosis of an iron deficiency anemia is incorrect or that there may be such a gross loss of blood that the body is unable to regenerate blood rapidly enough to overcome the anemia even under the optimum conditions of iron therapy. Ordinarily if iron is administered in the doses indicated, the hemoglobin should regenerate at an approximate rate of 1 per cent daily.

It should be emphasized that nothing can be added to iron which will enhance its effect importantly, although claims to this effect have been made repeatedly. Iron and iron alone is indicated in an iron deficiency anemia, and the addition of liver, stomach tissue, copper, or any other form of alleged adjuvant is of no practical value. Such combinations are important, however, from the standpoint of cost, as they are far more expensive than simple preparations of the metal.

It should be stated positively that the proper route to give iron is orally. Despite the claims to the contrary, gastrointestinal complaints do

not frequently arise from its use. If they do appear, iron can be given effectively in enteric-coated capsules, the dose may be reduced, or the preparation may be changed. While ferrous sulfate is the most satisfactory type of iron to give routinely, another useful form of iron is ferrous gluconate in doses of 0.6 gm. (10 gr.) three times daily, after meals. If this dosage causes untoward symptoms, the initial dose might be 0.6 gm. (10 gr.) daily with a gradual increase in amount to the optimum point of tolerance.

It is never my policy to administer iron parenterally. This is because I rarely have had serious difficulty in giving it by mouth, and if the proper amount is injected either intramuscularly or intravenously, serious and sometimes dangerous reactions may occur. If it is determined that iron cannot be taken orally after careful readjustment of the dosage and change of the preparation, consideration should be given to the administration of blood transfusions, if the severity of the anemia justifies such therapy. Not only will these transfusions supply blood to overcome the anemia, but 500 cc. of blood also contains about 250 mg. of iron, which is a sizeable intravenous dose.

THE MACROCYTIC ANEMIAS INCLUDING PERNICIOUS ANEMIA

A macrocytic anemia may be defined as one in which the red blood cells have a larger mean volume than normal, the color index is usually about 1.0 or higher, the immediate and primary cause of the anemia is usually a diminished rate of formation of the red blood cells in the bone marrow, and with few exceptions there is a gratifying response to antipernicious anemia medication, such as liver. Examples of such an anemia are true addisonian pernicious anemia; sprue; the anemia of widespread liver disease such as cirrhosis; the anemia in some cases of pellagra; in fish tapeworm infestation; following short-circuiting operations on the intestinal tract or stenosis of the intestines; some types of anemia of pregnancy and infancy; anemia due to diminished intake of "extrinsic fac-

tor"; anemia in association with destruction of the glands of the fundus of the stomach as may be seen following total gastrectomy, in linitis plastica, and in syphilis of the stomach.

The blood picture in such conditions is characterized by the presence of large, dark-staining, oval red blood cells which are designated as macrocytes. Also there may be small cells, microcytes, and many cells which are of abnormal shape, poikilocytes. These changes are more striking when the total red blood cell count is less than 2,500,000 per cubic millimeter. The mean corpuscular volume in such conditions is always greater than 100 cubic microns, and in some instances may reach 140 cubic microns or even higher. The mean corpuscular hemoglobin concentration is 30 per cent or more, and the color index is 1.0 or greater.

If a sternal puncture is done in such patients the characteristic finding is the presence of many large primitive red blood cells, called megaloblasts. This is interpreted to indicate that the red blood cells have failed to develop, in other words that a maturation arrest is present. A change such as this indicates that the red blood cells do not mature at the normal rate, consequently they are not released into the blood stream in the usual numbers and there is a decrease in the red blood cell count.

THE most commonly encountered macrocytic anemia associated with a maturation arrest, especially in the northern part of the United States, is true addisonian pernicious anemia. To illustrate the diagnostic features of such an anemia, the following patient is presented.

Mr. B. is 64 years of age and he considered himself to be in good health until about ten years ago. At that time he developed fatigability and weakness, dyspnea on exertion, palpitation, and his family told him he was developing pallor. The symptoms just stated are characteristic of an anemia, but they give no indication of the type. The following two complaints, however, are highly distinctive of pernicious anemia. He complained of periodic sore tongue, characterized by intervals of remission and exacer-

bation. This may occur in such conditions as pellagra, but it is always highly suggestive of pernicious anemia, as about two-thirds of such patients have this complaint. In addition, he noted almost from the onset of the present illness numbness and tingling of the extremities.

It may be stated positively that if a person of middle age or older complains of the general symptoms of anemia (weakness, ease of fatigue, dyspnea on exertion, palpitation, and pallor) and in addition has recurrent glossitis and paresthesia of the hands and feet, the diagnosis of pernicious anemia is almost certain, even before the blood is examined. If, in addition, he has a posthistamine achlorhydria, the diagnosis is practically assured. Other diagnostic points are the presence of a macrocytic anemia with a high color index, and the prompt response to anti-pernicious anemia therapy. Ten years ago, when this patient was first examined, he had a red blood cell count of 1,300,000 per cubic millimeter and a hemoglobin of 5.7 gm. (34 per cent). Following the institution of treatment with liver extract intramuscularly, there was a prompt improvement which has been maintained ever since by the weekly injections of this preparation.

THE second patient, Mr. M., age 66 years, illustrates that pernicious anemia is not only characterized by an anemia but also by involvement of the nervous system which in some instances, as in this patient, may dominate the clinical picture. This patient was well until about ten years ago when he developed difficulty in walking. His lower extremities became stiff and weak. These symptoms progressed to the point where it was impossible for him to stand, and he was confined to bed. With this, he experienced numbness and tingling of the hands and feet. This patient has not had severe anemia at any time. The lowest red blood cell count, which was in April 1937, was 3,900,000 per cubic millimeter and the hemoglobin was 15.0 gm., approximately 100 per cent. Gastric analysis showed no free hydrochloric acid.

I should like to emphasize that this patient

did not have the symptoms of anemia such as pallor, weakness, dyspnea, or palpitation, nor did he have recurrent glossitis. His presenting symptoms were referable to the nervous system, and were in the form of a spastic, ataxic paraplegia in association with paresthesia of the extremities. It is known that in pernicious anemia the nervous system may be involved in 90 per cent of the cases. In most patients, the damage is limited to a peripheral neuritis, causing numbness of the hands and feet. If the condition progresses further, there are degenerative changes in the posterior columns of the spinal cord producing ataxia. Finally, the lateral columns may become involved and this is responsible for the spastic paraplegia. In extreme examples of the disorder, there may be a loss of sphincter control.

This patient has been treated efficiently with intramuscular liver extract and has regained his ability to walk although he still uses a cane for support.

TREATMENT OF PERNICIOUS ANEMIA

The most satisfactory method of treating patients with pernicious anemia, or any type of macrocytic anemia with a megaloblastic bone marrow, is by the intramuscular injection of 1 cc. refined liver extract, containing 15 units, daily for a period of two weeks. At the end of this time I would give 1 cc. (15 units) three times weekly until the red blood cell count is at least 4,500,000 per cubic millimeter and the hemoglobin a minimum of 12 gm. (83 per cent). The maintenance dose, in my opinion, is 1 cc. (15 units) every two weeks, although some have stated that the blood may be maintained in a normal condition by giving such a dose once a month.

There is one danger which should always be kept in mind. If an inadequate dose of liver extract is employed, the red blood cell count and hemoglobin may fall below normal limits. Although there may be only a slight reduction, nevertheless there is always the possibility that nervous manifestations may develop, or if already present they may progress, sometimes

not frequently arise from its use. If they do appear, iron can be given effectively in enteric-coated capsules, the dose may be reduced, or the preparation may be changed. While ferrous sulfate is the most satisfactory type of iron to give routinely, another useful form of iron is ferrous gluconate in doses of 0.6 gm. (10 gr.) three times daily, after meals. If this dosage causes untoward symptoms, the initial dose might be 0.6 gm. (10 gr.) daily with a gradual increase in amount to the optimum point of tolerance.

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period of gestation. In studies done some years ago by Dr. Frank H. Bethell at the University of Michigan, the standards for the physiologic anemia of pregnancy were established. The normal decrease in the hemoglobin and red blood cells in pregnancy is due solely to an increase in the plasma volume and a dilution of the constituents of the blood. It was established that the lower limits of such an anemia were 10 gm. (64 per cent) of hemoglobin per 100 cc. of blood and 3,500,000 red blood cells per cubic millimeter. Before one can state, therefore, that an abnormal anemia of pregnancy is present, it must be shown that the hemoglobin is less than 10 gm., or that the red blood cell count is decreased below 3,500,000 per cubic millimeter, or that both conditions are present.

THE anemias of pregnancy are exceedingly common and are usually easily prevented. It has been determined that 54 per cent of supposedly healthy pregnant women observed in the obstetrical outpatient department of the University of Michigan Hospital had a significant anemia of pregnancy. Of these, 37 per cent were of the iron deficiency type, characterized by a microcytic, hypochromic anemia, and 15 per cent were of the macrocytic variety. In 12 per cent, the anemia was macrocytic and hypochromic, or the mixed type.

IRON DEFICIENCY ANEMIA OF PREGNANCY

In pregnancy there is a notable increase in the demands for iron due mainly to the following three reasons: (1) to supply fetal needs; (2) to form additional erythrocytes in an attempt to compensate for the dilution due to plasma volume decrease, and (3) to meet the requirements associated with the formation of the additional maternal tissue. It is estimated that the requirements of pregnancy are probably two or three times greater than the loss of the metal by normal menstruation over a corresponding interval. Undoubtedly one of the most important contributing factors to the iron deficiency anemia of pregnancy is the existence of a slight iron deficiency prior to

pregnancy which has caused a mild anemia. When the blood volume of the pregnant woman is increased, and reaches its maximum dilution of about 26 per cent at the beginning of the last trimester of pregnancy, the degree of anemia is accentuated. For example, if the hemoglobin was 70 per cent before pregnancy, the resultant hemoglobin reading would be 58 per cent when the maximum dilution effect comes into play.

MACROCYTIC ANEMIA OF PREGNANCY

The other important type of anemia of pregnancy is the macrocytic variety which usually manifests itself by a reduction in the red blood cell count to 2,500,000 or 3,000,000 per cubic millimeter with an associated hemoglobin reading of 50 to 60 per cent (7.8 to 9.4 gm.). The mean corpuscular volume in such patients is increased, often to the vicinity of 100 to 110 microns. In some instances, the red blood cell count may be as low as 1,000,000 per cubic millimeter and the peripheral blood display all the classical characteristics observed in true Addisonian pernicious anemia. This has been called "pernicious anemia of pregnancy." It differs from Addisonian pernicious anemia, however, in that free hydrochloric acid may be present in the gastric secretions, neurologic manifestations are not present, and the blood returns to normal after delivery. Furthermore, the anemia may not recur in subsequent pregnancies.

It has been found by Bethell and his associates¹ that there is an inverse relationship between the incidence of this type of anemia and the animal protein content of the diet. Such an anemia was not present in patients who had an animal protein intake of 50 gm. or more daily; with an intake of 30 to 49 gm. it was present in 10 per cent of his group of patients, and with an intake of 30 gm. or less, it was present in 14 per cent. It must be concluded, therefore, that the macrocytic anemia of pregnancy is in some way related to a deficiency of animal protein in the diet, but the exact nature of this relationship is at present obscure.

¹BETHELL, F. H., and BLECH, E.: The diet in pregnancy. *Clinics* 1:346-357, 1942.

with alarming rapidity. In general, it may be said that when the blood is kept in a normal condition, the nervous changes, if present, may improve greatly, or at least that they will not progress. If they are not present before treatment is started, they will not appear during the course of adequate therapy.

I do not advocate the use of dilute hydrochloric acid, as my patients appear to do as well without this form of medication as with it. Nor do I think it is usually necessary to give iron, although in an occasional patient the color index has remained low and has been brought to normal promptly with the addition of iron medication.

THERE is one point of practical importance which should be emphasized. In about 5 per cent of all patients who are treated over a considerable period of time with liver extract intramuscularly, allergic manifestations may develop. These range in severity from slight "stiffness" of the nose to outspoken anaphylactic shock. In the management of such conditions, a change in the brand of liver extract or reduction in the dose may give relief, or the medication may be shifted to the oral type using extralin in doses of three pulvules, three times daily. In some instances it has been necessary to desensitize the patient, which may be done as follows:

An initial subcutaneous injection of 0.1 cc. of a 1 to 10 dilution of liver extract is given, and this is increased by about 0.2 cc. every second or third day for about three weeks until the patient is receiving the full therapeutic dose of 1.0 cc. (15 units) of refined liver extract. When giving liver extracts to patients who may be sensitive to it, any untoward symptoms which arise immediately following the injection are readily controlled by the subcutaneous administration of 0.3 to 0.5 cc. of 1 to 1,000 solution of epinephrine chloride.

A final word of advice should be given concerning the use of liver extract or any other type of antipernicious anemia medication. Such medication will be of absolutely no value in

any patient unless an anemia is present, and unless the anemia is of the macrocytic type with a megaloblastic bone marrow. It is urged, therefore, that an exact diagnosis be made and the drug given only when the proper indications are present.

USE OF FOLIC ACID

Recently a considerable number of publications have appeared dealing with the use of folic acid, the newest component of the vitamin B complex, as a form of treatment for macrocytic anemias of pernicious anemia type. Experience, however, tells us unquestionably that such treatment is inferior to the use of liver extract and should not be substituted for it, for two reasons: (1) Although it produces a satisfactory increase in the red blood cell count of many patients with pernicious anemia, in some it will not bring the count completely to normal. In others the red blood cell count may reach normal but not be maintained there despite continued use of the drug in what is considered adequate doses; (2) It has now been determined that folic acid has little, if any, effect on the nervous manifestations of pernicious anemia. In my opinion its continued use in pernicious anemia is contraindicated. On the other hand, it appears to be effective when given orally in doses of 15 to 20 mg. in the treatment of sprue, the macrocytic anemia of pregnancy and infancy, and possibly liver disease. In such conditions, neurologic involvement does not complicate the clinical picture.

ANEMIAS OF PREGNANCY

I should like to conclude my discussion with some remarks on the anemias of pregnancy. These are important because they are common, and in most instances are readily controlled by simple measures.

A true anemia of pregnancy may be defined as one due primarily to the gravid state in which there is a decrease in the hemoglobin and red blood cell count, or both, below the diminished levels regarded as normal for the

period of gestation. In studies done some years ago by Dr. Frank H. Bethell at the University of Michigan, the standards for the physiologic anemia of pregnancy were established. The normal decrease in the hemoglobin and red blood cells in pregnancy is due solely to an increase in the plasma volume and a dilution of the constituents of the blood. It was established that the lower limits of such an anemia were 10 gm. (64 per cent) of hemoglobin per 100 cc. of blood and 3,500,000 red blood cells per cubic millimeter. Before one can state, therefore, that an abnormal anemia of pregnancy is present, it must be shown that the hemoglobin is less than 10 gm., or that the red blood cell count is decreased below 3,500,000 per cubic millimeter, or that both conditions are present.

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pregnancy which has caused a mild anemia. When the blood volume of the pregnant woman is increased, and reaches its maximum dilution of about 26 per cent at the beginning of the last trimester of pregnancy, the degree of anemia is accentuated. For example, if the hemoglobin was 70 per cent before pregnancy, the resultant hemoglobin reading would be 58 per cent when the maximum dilution effect comes into play.

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TREATMENT OF THE ANEMIAS OF PREGNANCY

BECAUSE the anemias of pregnancy are common, it is my opinion that proper preventive measures should be instituted at the earliest possible moment after pregnancy is recognized. This may be accomplished by the following two simple measures: (1) the administration of 0.3 gm. (5 gr.) of enteric-coated ferrous sulfate tablets, three times daily, following meals, and (2) measures to provide an adequate amount of animal protein in the diet. The latter may be assured if a minimum of one quart of milk, a serving of lean meat, and one egg are given daily. If there should be difficulty in taking the iron medication, and in our experience this has been rare even during pregnancy, ferrous gluconate in doses of 0.6 gm. (10 gr.) may be administered three times daily following meals, or if necessary the dose may be reduced one-third and then cautiously increased.

The importance of these simple measures cannot be overestimated. By their use over 90 per cent of all anemias of pregnancy can be prevented or controlled. Thus, lactation is often possible when otherwise it would not be, convalescence is expedited, puerperal infection is less likely, and the child will be born with adequate iron reserves. If adequate treatment is not given, the blood of the infant might be normal at birth, but an iron deficiency anemia is likely to develop during the first year of life.

In the presence of a severe macrocytic anemia, it may be advisable to consider the possibility of blood transfusions as an emergency measure to avert serious immediate consequences to the mother. The patient can also be treated with liver extract intramuscularly in the dosage given in the section on the treatment of the macrocytic anemias, or folic acid may be employed

orally in doses of 15 to 20 mg. daily. Our experience with the latter drug, however, is insufficient to render a final opinion concerning its efficacy at present.

ASSOCIATION OF BLOOD DISORDERS
WITH PREGNANCY

Occasionally a patient with a blood dyscrasia of one type or another becomes pregnant. The situation then is one in which a blood condition coexists with the pregnancy and has no direct etiologic relationship to it. Each condition might, however, have an important influence on the other. In a number of patients with pernicious anemia I have observed a pregnancy carried through successfully to term and a healthy child born. Certainly there is no indication to terminate a pregnancy in a woman who has this type of blood disorder, provided the blood is maintained at a normal level by treatment with intramuscular liver extract.

It is also possible for a woman to go through pregnancy successfully even though she may be suffering from a chronic leukemia. In such patients, however, roentgen ray or radioactive phosphorus therapy should be withheld in order to avert serious monster-like changes in the child. It does no harm, however, to give such a patient repeated blood transfusions; in fact they are advisable if an anemia is present. It is probably wise, however, to defer treatment with arsenic in the interest of the fetus.

It is thought by some that the rare association of pregnancy with aplastic anemia is an indication for therapeutic abortion. I have had no experience with this situation but I would advise repeated blood transfusions before considering interruption of the pregnancy.

Osteopathies Encountered in the Endocrine Clinic

RITA S. FINKLER, M.D., AND GEORGE M. COHN, M.D.

ENDOCRINE SERVICE OF THE NEWARK BETH ISRAEL HOSPITAL
NEWARK, NEW JERSEY

The following cases have been grouped because each exhibits the common denominator of some form of bone pathology, though these patients were first referred to the Endocrine Service under the assumption that they presented some endocrine pathology. In some of the cases, the etiology could be assumed to be definitely of an endocrine dysfunction; in others, no definite endocrine etiology could be demonstrated.

Though there are a relatively large number and variety of osseous endocrine disturbances, we have presented only the following seven cases, because of space limitations and greater general interest in these conditions. We have included also a comprehensive differential diagnosis of these related conditions in the form of a table.

The following cases will be presented:

1. Hypothyroidism with Osteoporosis
2. Pituitary Adenoma with Acromegalic Manifestations
3. Turner's Syndrome
4. Lorain-Levi Dwarfism
5. Pseudo Froehlich's Syndrome with Osteogenesis Imperfecta
6. Hypogonitalism with Fibrous Dysplasia of Bone
7. Macrosomia Genitalis with Accelerated Bony Maturation

This exhibit, originally presented at the June 1947 meeting of the A.M.A. in Atlantic City, was made possible through a grant from the Schering Corporation, Bloomfield, N.J. We wish to thank Dr. W. H. Stoner for his generous cooperation in the preparation of the exhibit and for supplying the Progynon-B and Oretan used in the treatment of our cases.

HYPOTHYROIDISM WITH OSTEOPOROSIS

E. S., a 16-year-old white girl, was referred to the Endocrine Service in 1938 by the Orthopedic Service, because of waddling gait, peculiar body configuration and amenorrhea.

The physical examination revealed a white obese girl with peculiar posture when standing; pale, puffy skin and coarse hair. The external genitalia and secondary sex characteristics were underdeveloped for her age.

The patient was sluggish and mentally retarded.

The x-ray of the hips, long bones and skull showed osteoporosis of all cancellous bone with thinning of the cortices, and a developmental anomaly of the heads of the femora with flattening at the superior surfaces and broadening and foreshortening of the necks so that the greater trochanters were relatively elevated; there was evidence of delayed epiphyseal union.

The laboratory findings were as follows:

B.M.R.—Minus 33 and Minus 30%

Blood Chemistry:

Urea nitrogen—18.8-17 mg.%

Creatinine—1.4 mg.%

Cholesterol—428 mg.%

Sugar—71 and 79 mg.%

Calcium—10.3 and 10.7 mg.%

Phosphorus—4.7 mg.%

Phosphatase—3.4 Bodansky U.

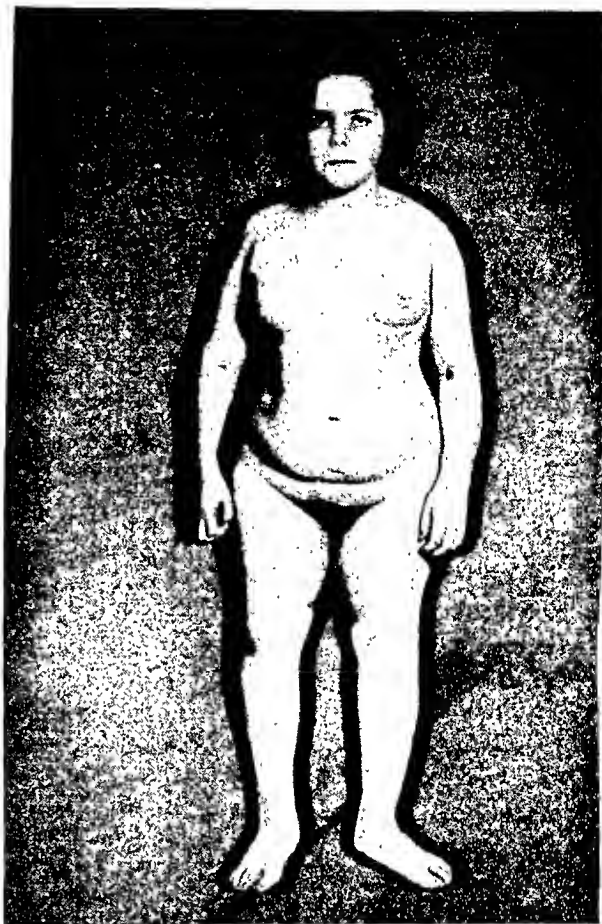
Glucose Tolerance:

Min.	Blood	Urine
0	83 mg.%	0
30	125 mg.%	0
60	158 mg.%	0
120	200 mg.%	0
180	125 mg.%	0

Urinary Bio-assays:

Estrin—3 to 15 R.U./L

Gonadotrophin—0 to 10 m.u./L



Age 17; height 55¾"; weight 138½ lbs.

A point of interest is the developmental anomaly of the heads of the femora, which resembled Legg Perthe's disease, but is actually due to deficient calcium content of the bones and delayed epiphyseal development and not erosion of the articular surfaces.

The roentgenological findings, low metabolic rate, the high cholesterol values, together with the physical appearance of myxedema and mental sluggishness present a complete picture of hypothyroidism.

The patient was placed on desiccated thyroid substance and satisfactory progress was reported periodically by the patient's local physician.



Knee. Osteoporosis, striations, cortical thinning; delayed epiphyseal union.

DISCUSSION

Hypothyroidism, which is due to absence or inadequacy of the thyroid gland, may be the result of developmental anomalies, infection,

inflammation, atrophy, degeneration or surgical removal or may be secondary to pituitary deficiencies.

Congenital aplasia may not be recognized at birth or early infancy but becomes evident in early childhood. General myxedema, which usually follows surgical removal or degeneration of the thyroid gland is familiar to all. Adolescent hypothyroidism may occur in mild or severe form and manifests itself by delayed growth and ossification. There may be some mental and sexual retardation. Non-myxedematous hypothyroidism of the adult is either a continuation of the adolescent hypothyroidism or may be acquired by a previously normal adult. Secondary hypothyroidism associated with dysfunction of the pituitary gland is due to hyposecretion of the thyrotrophic hormone by the anterior pituitary gland. The patient usually shows symptoms of hypopituitarism with some features of hypothyroidism.

Therapy generally consists of administering adequate doses of desiccated thyroid substance early enough to prevent the irreversible changes, which may occur in untreated cases of hypothyroidism. The results are usually favorable and can be maintained under sustained medical supervision.



Pelvis and femora. Osteoporosis, delayed development of epiphyses; flattening of epiphyseal heads.

PITUITARY ADENOMA WITH ACROMEGALIC MANIFESTATIONS

Mrs. D. S., age 46, came to the Endocrine Clinic in 1937 with complaints of bitemporal headaches, generalized arthritic pains, swelling of the face, lips, tongue, hands and feet. For a period of six years prior to admission the patient had noted that she began to require gradually larger sized shoes and that the outline of her face also became larger. The patient had received several courses of radiation therapy to the region of the pituitary gland at the Newark City Hospital prior to admission to the Endocrine Clinic.

Laboratory findings showed apparently normal blood chemistry, glucose tolerance curve, B.M.R., and C.B.C., but the x-ray of the sella turcica showed evidence of a pituitary tumor and urinary bio-assays revealed about 400 m.u./L of gonadotrophins (*F.S.H.*). Since there were no visual disturbances, it was decided (after neurological consultation) not to attempt surgery.

The patient was placed on intensive estrogenic therapy and showed marked improvement in symptoms. Bio-assays showed a fall in the urinary gonadotrophin to 100, 50 and 5 m.u./L. Cessation of estrogenic therapy resulted in a recurrence of the symptoms and a rise in urinary gonadotrophin.

Several successive series of radiation therapy resulted in only slight and temporary improvement in symptoms.

Since large doses of estrogens were required to control symptoms of headaches, vertigo and edema of hands, face, tongue and lips, implantation of Estradiol pellets (90,000 R.U.) was carried out. The relief afforded by this therapy lasted for about 3 months. It was estimated that the body utilized about 7,000 R.U. per week while by injection 20,000 to 30,000 R.U. had to be given for equal relief of symptoms. Since the



Age 46; height 61"; weight 161 lbs.

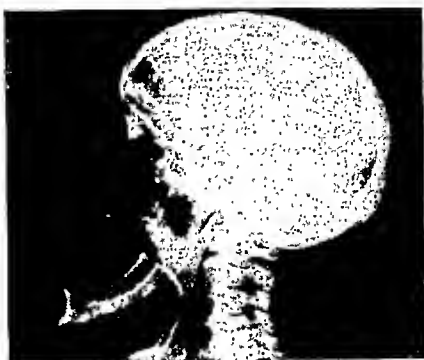
beginning of this form of therapy in 1940, the patient has required the implantation of 50 mg. of Estradiol every 3 to 4 months for control of symptoms.

Follow-up examinations over a period of 10 years have shown no changes in visual fields nor any evidence of pressure on the optic chiasm, while the x-rays of the sella turcica show only slight increase in depth.

It is quite evident that high dosage estrogenic therapy is the treatment of choice in this case, and should be considered in other similar cases.



1937. Before therapy. Enlarged sella turcica; erosion of anterior wall.



1947. After 10 years of Progynon-B parenterally and estrogen pellet implantation. No increase in erosion; slight increase in depth of sella.

DISCUSSION

Acromegaly is a disease of adult life, characterized by hypertrophic osseous and soft tissue changes of the face, hands, feet and thorax. It is caused by an eosinophilic adenoma of the anterior pituitary gland with excessive production of anterior pituitary hormones. This is followed by secondary overactivity of the thyroid, parathyroid and adrenal glands. Atrophic changes in the gonads and secondary amenorrhea in the female are frequently encountered, though testicular atrophy in the male is rather uncommon.

Laboratory studies usually reveal glycosuria, hyperglycemia and a diminished glucose tolerance; disturbed calcium-phosphorus metabolism due to secondary hyperparathyroidism and excretion of abnormal amounts of pituitary gonadotrophin.

Radiation and hormonal therapy are of great value in selected cases. Estrogens are used in the female and androgens in the male because of their inhibitory action on pituitary activity. Surgery is indicated only in the presence of a suprasellar cyst or in progressive loss of vision due to pressure on the optic chiasm.

TURNER'S SYNDROME

E. A. presented herself in 1940 at the age of 20 with complaints of amenorrhea, stunted growth, retarded development of secondary sex characteristics, and thickening and shortening of the neck.

The family history and past history were essentially negative except that after the age of 5, the growth rate slowed down greatly so that the patient grew only $4\frac{1}{2}$ inches during the last 10 years.

Physical examination revealed a short, underdeveloped, white female $57\frac{1}{4}$ inches tall and weighing $97\frac{1}{2}$ lbs. Webbing of the neck and some slight retraction of the head were evident. There was no development of any of the secondary sex characteristics except some sparse pubic hair, which had appeared after a series of estrogenic injections given by the family physician. External genitalia, and adnexa, were infantile in their development.

Laboratory and x-ray findings were essentially negative except for increased urinary gonadotrophin and some osteoporosis.

The patient was placed on a schedule of estrogenic therapy whereby she received 10,000 R.U. of Estradiol Benzoate every third day for 5 injections followed by a rest period of 2 weeks. This form of therapy was carried out for about 1½ years during which time the patient had cyclic bleeding and developed all the secondary sex characteristics. Subsequently, the patient was placed on oral stilbestrol 2 mg. daily for 2 to 3 weeks followed by periods of rest to allow for withdrawal bleeding. Monthly cyclic bleeding occurred as long as therapy was continued and there was further development of breasts and pubic and axillary hair, although the height remained stationary.

Psychologically the patient showed a marked improvement in personality. She changed from a shy depressed individual to a social and cheerful person and now holds a responsible business position.

DISCUSSION

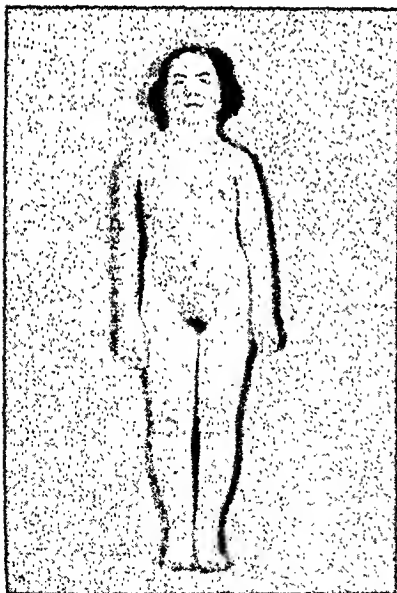
The syndrome described by Turner in 1938 is characterized by short stature, juvenile body configuration, failure of secondary sex characteristics, primary amenorrhea, webbed neck and cubitus valgus and is caused by primary ovarian agenesis. Although the neck is apparently short, the number of cervical vertebrae is normal.

Bio-assays of the urine reveal the absence of estrogenic activity and the presence of excessive amounts of pituitary gonadotrophin. Vaginal smears reveal an absence or minimum of follicular activity.

Histological examination of ovarian tissue, when available, shows ovarian agenesis.

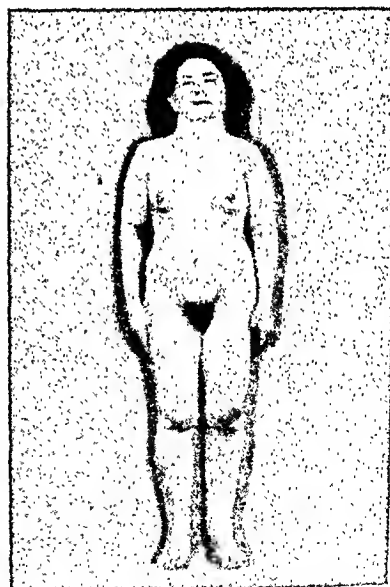
Pituitary hormones are of no avail. Substitution therapy with estrogenic hormones causes development of the secondary sex organs.

Uterine bleeding can be induced and maintained cyclically by estrogenic therapy.



Age 20; height 57¼"; weight 97½ lbs.

Lateral view of neck; moderate osteoporosis.



Age 25; height 57½"; weight 112 lbs. after Progynon-B and stilbestrol therapy.

LORAIN-LEVI DWARFISM



Age 17; height 42½"; weight 38 lbs.

R. J., who was one of 4 children, presented himself at the Endocrine Clinic in 1942 at the age of 13 with the complaint of retarded growth. His father and mother were above average height, and the siblings were all apparently normal.

The patient was a full-term baby, who displayed some delayed physical development in that dentition and walking were delayed. At age 5, the patient stopped growing, though intellectually he kept up with the other children of his age. Scholastic standing was high.

Examination revealed a small male propor-

tionately developed; height 40 inches, weight 34 lbs.; and external genital development in keeping with his size. The mental attitude was keen and alert.

Laboratory findings were essentially negative. X-rays showed a congenitally small sella turcica and delay in epiphyseal union and development of ossification centers of the bones of the hands and wrists with a bone age of about 3 years.

The patient refused treatment and did not return again until 1946, at the age of 17, at which time his height was 42½ inches and weight 37½ lbs. The x-rays showed an advance in bone age to about 4 to 5 years, while the external physical findings were essentially the same as at the first visit in 1942.

Infantile body proportions, and genital development, high pitched childish voice, and an alert, critical mind were present.

Testosterone was the therapy of choice and may have resulted in some increase in height and probably in genital development but was refused by the patient.

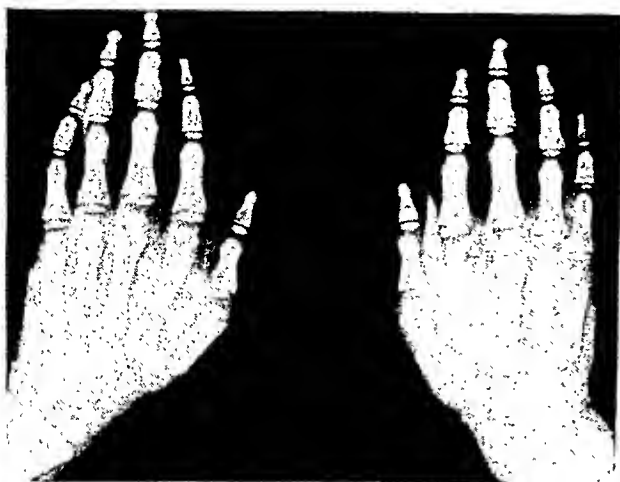
By virtue of his developmental anomaly, he holds the position of an usher.

DISCUSSION

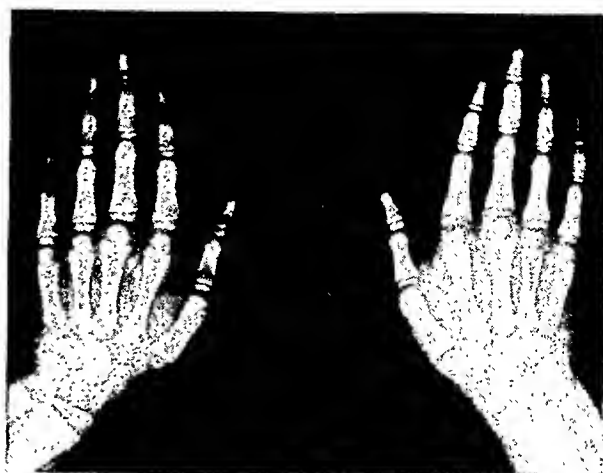
The Lorain-Levi type of dwarfism represents the classical picture of pituitary dwarfism. It may be congenital but usually is the result of an infection of the anterior lobe of the pituitary gland, which may occur during some infectious disease of childhood.

The pituitary dwarf has a diminutive and well proportioned body; the features are small and doll-like and the skin is soft and delicate.

There is usually a low fasting blood sugar and greatly increased glucose tolerance. X-rays of the bony frame and the head show retarded development of ossification centers and mark-



1942. Hands and wrists (age 13) delayed epiphyseal union; delayed formation of centers of ossification, only three carpal bones being present. Bone age—3 years.



1946. Hands and wrists (age 17) no change in epiphyseal union; slight progress in formation of centers of ossification. Bone age between 4 and 5 years.

edly delayed epiphyseal union, small cranium with face disproportionately small, thin calvarium, hypoplastic or absent frontal sinuses, small and dense mastoids and small sella with closely approximated clinoid processes. All other laboratory findings are within normal limits.

Specific therapy has been unsuccessful. Growth hormone and pituitary factors have not given satisfactory results. Supportive treatment with thyroid, vitamins, minerals and a nourishing diet is required. Gonadotrophin, androgens and anterior pituitary gland implants are worthy of consideration.

PSEUDO-FROEHLICH'S SYNDROME WITH OSTEOGENESIS IMPERFECTA

J. J. was first seen in 1942 at the age of 10 with a history of frequent spontaneous fractures which began to occur shortly after birth in various parts of the body and required confinement to bed and the use of braces.

The patient was under constant medical supervision and received various forms of vitamin, mineral and nutritional therapy without any influence on the course of the disease.

Examination revealed a plump, cheerful youngster apparently well adjusted, with definite bluish sclerae and marked deformity of both lower limbs and the torso.

Laboratory findings were within normal limits, but the x-ray examinations showed a large skull with absence of normal bone structure, hair-like striations of the bones of the vault

and a sella turcica that was 50% undersize. The thorax showed multiple healed rib fractures, osteoporosis of the long bones and pelvis, thinning and vacuolation of the cortices of the long bones and bowing of the femora.

The patient was placed on sustained vitamin D and calcium therapy, but fractures with subsequent healing continued to occur at intervals. In 1947, at the age of 14½ years, the patient showed a marked diminution of the bluish tinge of the sclerae and for the last 10 months had had no further fractures.

The disease is due to a defect in mesenchymal development and is essentially a deficiency of osteoid structure caused by defective osteoblastic activity. The disease is known to be hereditary and is frequently accompanied by deafness



Age 10; height 43"; weight 67½ lbs; blue sclerae.

though both of these features were absent in our patient. The disease tends to be self-limiting, and arrest of the pathological process and healing usually takes place after maturity.

Therapy consists of nutritional adjustment, calcium and vitamin D therapy and mechanical support.

Testosterone therapy may be considered as a means of stimulating maturity.

DISCUSSION

Osteogenesis imperfecta is a disease of the bony structures characterized by a deficiency in the number and function of the osteoblasts and thought to be some form of endocrine disturbance. It manifests itself by a familial hereditary tendency, although it has been known to occur in a single individual in whose family there is no history of its occurrence.

Clinically, there are marked osseous deform-



Pelvis. Osteoporosis; cystic formation in cancellous portion of bone.

ities throughout the body, particularly bowing of the legs, occasional deafness and blue sclerae.

Except for x-ray findings, laboratory findings are usually within normal limits.



Lower extremities. Osteoporosis; deformity of femurs, tibiae and fibulae; tendency to cystic formation in cancellous portion of bones.

HYPOGENITALISM WITH FIBROUS DYSPLASIA OF BONE

L. G., who is now 19 years old, was first referred to the Endocrine Clinic at the age of 13 after having been under intermittent observation at the orthopedic clinic where he had been seen for a post-fracture deformity and paresis of the right arm. In the course of x-ray investigations, the peculiar trabeculated and cyst-like appearance of the bone was noted. A biopsy of a right radial exostosis showed the histological appearance of fibrous tissue, infiltrating cancellous bone. A diagnosis of fibrous dysplasia of bone was confirmed by H. L. Jaffe of New York.

A feature of this case was the prominent enlargement of the right malar and orbital region. The patient complained of progressive loss of vision in the right eye and ophthalmologic examination showed evidence of choked disc, but no defect in the visual field. The left eye was normal. It was felt that there was bony and fibrous encroachment upon the right orbital contents and surgical intervention was considered, but was not attempted after consultation with the neuro-surgeon because of the extreme technical difficulties and dangers.

Meanwhile, successive x-rays of the affected bones showed progression of the disease.

In a review of the few reported cases it was noted that the condition appeared in less severe form in the older patients than in the young ones and it was suggested that possibly somatic maturation might have some influence in the apparent arrest or retardation of the disease. On this basis, the patient was given testosterone propionate over a period of one year in an attempt to bring about an earlier maturation. During this time it was noted that high phosphatase values were obtained suggestive of stimulated bone-forming activity. Also, successive x-rays showed that a relatively short time after the initiation of therapy, a slowing of the process began and was eventually arrested with some regression of the lesions and an appearance of return to normal bone.

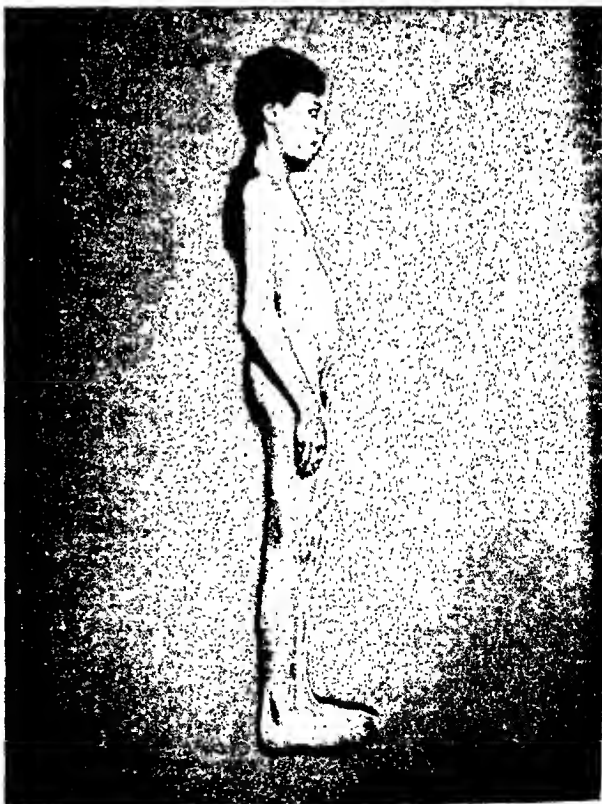
The patient has been without any treatment

for the last 4½ years and comparative x-rays taken at six to 12 month intervals indicate that the greatest amount of response occurred during and shortly after therapy.

DISCUSSION

Fibrous dysplasia of bone, formerly known as polyostotic fibrous dysplasia as described by Lichtenstein and Jaffe and by Albright and his associates, consists of typical bone pathology and distinct clinical features. It is assumed to be a congenital perversion of mesenchymal activity and is a chronic slowly developing disease which tends to become stabilized as the patient grows older.

The clinical appearance of the patient may not present any distinctive features, and diagnosis may be made by the radiological, histo-



Age 13; height 63"; weight 84 lbs. Before testosterone therapy.



1942. *Left humerus.*



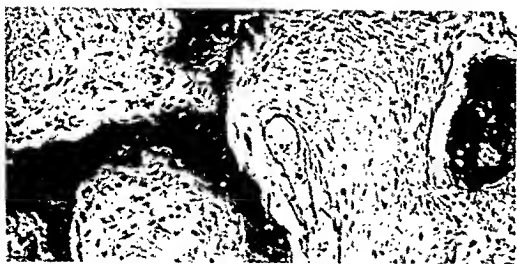
1942. *Progressive activity with fibrous infiltration. Thinning of cortices and hyperostosis of skull.*



1947. *Left humerus.*



1947. *Improvement and regression of fibrous infiltration with structural detail of bone returning to normal.*

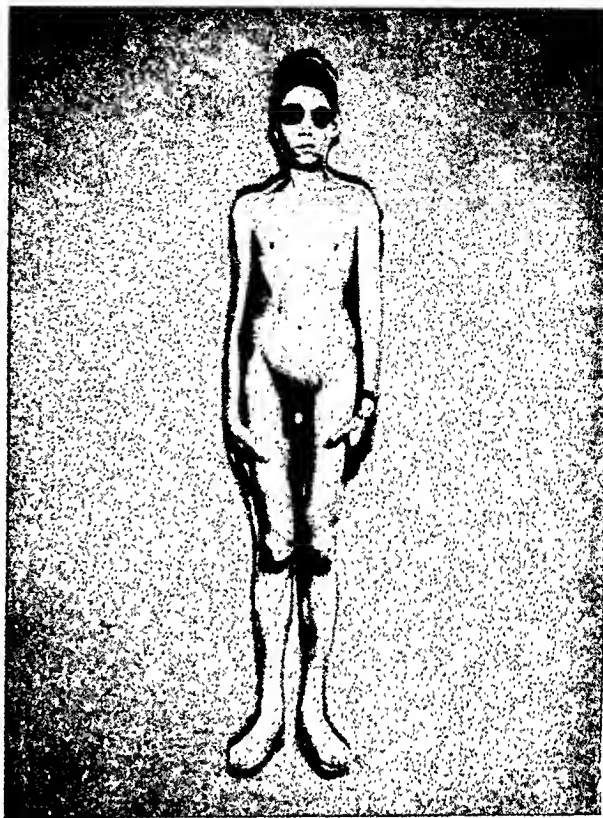


Age 10. Upper portion of radius. Cancellous bones showing fibrosis of marrow spaces and bone resorption with fibrous infiltration.

logical and blood chemistry studies. Special clinical features consist of pathological fractures, facial and skull deformities, areas of brown pigmentation and precocious puberty in the female.

The bone pathology is essentially an osteitis fibrosa disseminata. The disease may be unilateral or may involve many bones in the body. Normal and abnormal bone may be found in close proximity. Except for histological and radiological findings typical of the fibrous bone dysplasia, laboratory findings are essentially within normal range.

There is no known treatment, but in this case, the experimental use of testosterone propionate parenterally was apparently successful in causing arrest and some regression of the disease.



Age 15; height 69½"; weight 114 lbs. After year of testosterone therapy.

MACROSOMIA GENITALIS WITH ACCELERATED BONY MATURATION

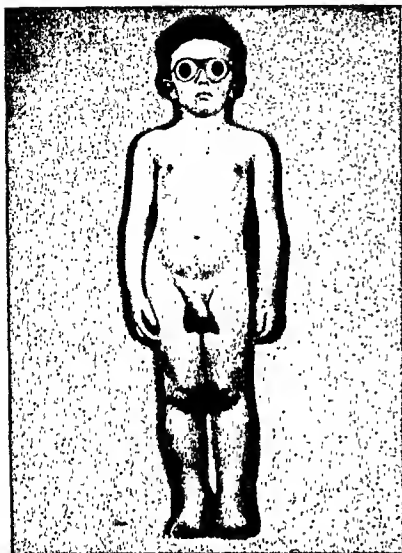
D. F. was first seen in 1943 at the age of 5 years, because of excessive sudden growth of external genitalia, frequent erections and emotional instability. The family history and past history were essentially negative except that a short time before the complaints became apparent, the patient had had measles accompanied by prolonged hyperpyrexia and had also sustained a blow on the back of the head as a result of a fall.

Examination was essentially negative except for the excessive genital development, and frequent and prolonged erections. X-ray findings

of the skull, spine, adrenal region, hands and wrists were negative or within normal limits for the age.

The patient was given stilbestrol, 1 mg., orally twice a day with subsequent reduction in the number of erections, slight regression in external genitalia and diminution in restlessness and belligerency. The dose was reduced to 0.5 mg. daily, when a slight gynecomastia developed. When therapy was discontinued, the original symptoms recurred.

Two months later, the patient was admitted to the New York Neurological Institute. All



11-15-43. Age 5; height 44"; weight 48 lbs.

the laboratory findings including x-ray studies, electroencephalogram, pneumoencephalogram, estimation of urinary 17-keto-steroids and bilateral airograms were within normal limits.

Radiation therapy to the pituitary and hypothalamic region was given in April and June 1944 without any apparent immediate effect.

However, subsequent examination showed a slight regression in the genitalia and almost complete cessation of erections. His cooperation and disposition improved greatly. The skeletal growth progressed rapidly, out of all proportion to age.

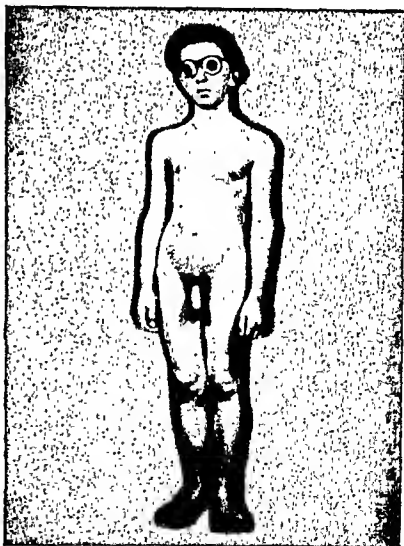
X-ray examinations of the hands and wrists at the chronological age of $7\frac{1}{2}$ years showed a bone age of about 11 years. There was also a marked increase in height; in $2\frac{1}{2}$ years the patient had grown almost 13 inches.

Pubertas praecox is usually described as re-

sulting either from the presence of an adrenal cortical tumor or a pineal tumor. However, tumors or changes in the morphological structure of the pituitary-hypothalamic region have been known to cause precocious puberty, and since the patient had a fall striking his head and later suffered an attack of measles with severe hyperpyrexia, it is possible to conceive that some disturbance had taken place in the diencephalon.

No therapy has been administered in the last 3 years. The physical and mental development are progressing normally and there has been no further progress in the growth of the genitalia. There has been no development of facial, body or axillary hair.

The voice, however, is somewhat lower than noted three years ago.



3-22-46. Age $7\frac{1}{2}$; height 56½"; weight 80 lbs.

DIFFERENTIAL

DISEASE	1 ALBRIGHT'S SYNDROME (Albright, et al.) Osteitis Fibrosa Disseminata	2 FIBROUS DYSPLASIA OF BONE (Lichtenstein and Jaffe)	3 OSTEITIS FIBROSA CYSTICA Osteitis Fibrosa Generalisata (Hyperparathyroidism)	4 PAGEY'S DISEASE	5 OSTEOMALACIA AND RICKETS (Juvenile osteomalacia)	6 POST-MENOPAUSAL OSTEOPOROSIS
ETIOLOGY	Embryonal disturbance, possibly of a trophic or neurogenic nature	Congenital perversion of mesenchymal activity	Parathyroid adenoma	Unknown	Deficient calcium deposition in bone matrix due to faulty intestinal absorption of calcium and phosphorus Urinary calcium loss due to deficient acid excretion in renal disease	Estragen deficiency
SPECIAL SIGNS	1. Pathological fractures 2. Unilateral bone involvement (usually) 3. Pigmentation on the affected side 4. Precocious puberty in the female	1. Pathological fractures 2. Facial asymmetry	1. Pathological fractures 2. Kyphosis and other deformities 3. Renal involvement	1. Asymmetrical increase in head volume 2. Bowing of tibiae, occasionally femora 3. Kyphosis 4. Occasional deafness or blindness (bone encroachment)	1. Bowing of extremities 2. Kyphosis 3. Softening of the pelvis 4. Bending and crumbling of the sacrum	Pathological fractures involving particularly the spine
BONE PATHOLOGY	1. Osteitis fibrosa 2. Replacement of bone by fibrous connective tissue 3. Thinning of the cortex of long bones due to endosteal erosion and marrow space distension by fibrous connective tissue 4. Pseudohypertrophy of bone 5. Enlargement of skull due to fibrous connective tissue and osteoblastic activity 6. Trochilated appearance of bone 7. Normal and abnormal bone may be contiguous		Generalized fibrocystic changes and bone decalcification and vacuolation	1. Characteristic structure of the skull: thickening and cotton-wool appearance due to irregular islands of rapid bone formation and resorption 2. Hyperostosis 3. Osteoporosis 4. Histology: Typical mosaic bone structure	1. Bone decalcification 2. Symphysiolysis 3. Thinning of the cortices of long bones 4. Bone absorption	Decalcified bone especially in spine and pelvis
BLOOD CALCIUM	Normal	Normal	Increased	Normal	Decreased or Normal	Normal
BLOOD PHOSPHORUS	Normal	Normal	Decreased	Normal	Decreased	Normal
BLOOD ALKALINE PHOSPHATASE	Normal or Increased	Normal or Increased	Increased	Increased	Increased	Normal
BLOOD CHOLESTEROL	Normal	Normal	Normal	Normal	Normal	Normal
THERAPY	Supportive measures Bone surgery	Bone surgery Testosterone therapy	Excision of parathyroid tumor	Supportive	Supportive	Estragen with or without testosterone High protein diet Mechanical support

ADDENDA—Increase in the enzyme, alkaline phosphatase, is in direct proportion to the stimulus of new bone formation (osteoblastic activity); in Osteitis fibrosa cystica, in Pagey's disease and in Osteomalacia it is always elevated; in Polyostotic fibrous dysplasia and in

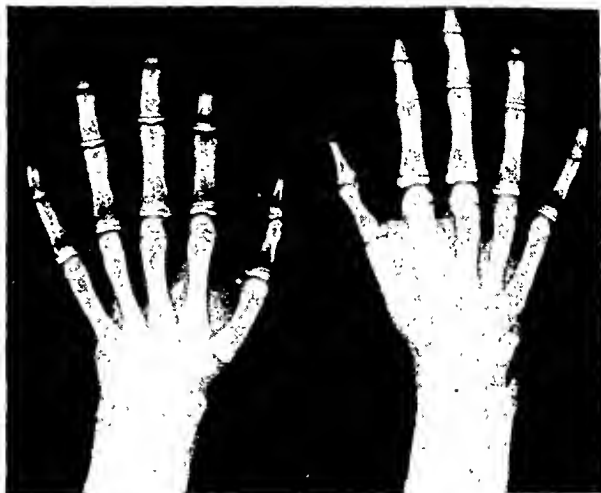
DIAGNOSIS

7 OSTEOGENESIS IMPERFECTA FRAGILITAS OSSEUM Lobstein's Disease	8 TURNER'S SYNDROME	9 HYPOTHYROIDISM Thyro-pituitary Dysfunction	10 ACROMEGALY	11 DWARFISM (Lorain-Levi Type)	12 MACROSOPIA GENITALIS JUVENILIS (Pubertas Praecox)
Deficiency of osteoid Defect in mesenchymal development Hereditary tendencies	Congenital ovarian agenesis	Thyroid deficiency	Pituitary adenoma (Eosinophilic adenoma of anterior pituitary)	Congenital defect	Morphologic alterations in diencephalon or adrenal tumor
1. Blue sclerae 2. Multiple spontaneous fractures 3. Ocasional deafness 4. Bowing of the legs 5. Extreme thinning of fibulae	1. Dwarfism 2. Somatic infantilism 3. Webbed neck 4. Cubitus valgus 5. Coarctation of aorta and other congenital anomalies 6. Normal mental development	1. Cretinism 2. Myxedema	1. Acromegalic facies 2. Acromegalic extremities 3. Double hunchback 4. Joint hypertrophy especially in the knees	1. Somatic and genital infantilism 2. Normal mental development	1. Rapid growth and development of external genitalia and gonads 2. Precocious muscular and osseous growth
1. Generalized osteoporosis 2. Thinning of bone cortex 3. Cystic formation in the cancellous portion of the bones (vacuolation) 4. Thickening of periosteum	Osteoporosis due to a disorder of tissue metabolism resulting in an underactivity of the osteoblasts	1. Growth retardation at epiphyseal cartilages 2. Delayed appearance of centers of ossification 3. Osteoporosis 4. Impairment of normal endochondral bone formations at heads of femora (resembling Osteochondritis juvenile deformans)	1. Deepening and erosion of the sella turcica 2. Thickening of the bones of the face and extremities	1. Delayed epiphyseal union 2. Delayed appearance of centers of ossification	Precocious bone maturation
Normal	Normal	Normal	Normal	Normal	Normal
Normal	Normal	Normal	Normal	Normal	Normal
Normal or increased	Normal	Normal	Normal	Normal	Normal
Normal	Normal	Increased	Normal	Normal	Normal
1. Calcium and vitamin D therapy 2. Mechanical support 3. Osteoplasty	Estrogenic therapy	Desiccated thyroid substance	Estrogenic or androgenic therapy Radiation therapy Surgery	Growth hormone or testosterone therapy	Estrogenic therapy Radiation therapy Excision of tumor if present

Osteogenesis imperfecta it may be normal or elevated according to the level of osteoblastic activity at the time of the study. Pituitary Gonadotrophin is present in the urine in Pituitary adenoma and in Turner's syndrome because of compensatory pituitary over-activity.



11-16-43. Development, ossification centers, carpal bones normal for age 5.



5-21-46. Bone age about 10-11 years; bone development advanced by 3 years.

DISCUSSION

Macrosomia genitalis or precocious puberty occurs in the female as well as in the male and consists of precocious somatic and genital development. It may be the result of neoplasms, infections, or constitutional developmental causes.

Recent advances in the scope of laboratory investigations have facilitated the differential diagnosis of causative factors in this condition. Routine laboratory tests are usually within nor-

mal limits except for x-ray findings of advanced bone maturation.

In the presence of a demonstrable cerebral, adrenal or testicular neoplasm, surgery is indicated. When structural changes in the hypothalamus or in the floor of the third ventricle are suspected, radiation therapy may be applied experimentally. Estrogenic therapy is of value in suppressing annoying erections, in allaying irritability and in arresting and partially correcting exaggerated genital development.

INTERNATIONAL ASSEMBLY

Public Auditorium

Cleveland, Ohio

November 9 to 12, inclusive, 1948

Thirty-third Year

The Medical Bookman

THE FOOT AND ANKLE*

THIS is the third edition of Dr. Lewin's definitive volume on the foot and ankle. As stated in the preface to the first edition, "The purpose of this book is to guide the student, general practitioner, industrial surgeon, and younger orthopedic surgeon in the diagnosis and treatment of diseases, deformities, and disabilities of the foot and ankle."

The latest edition accomplishes this aim even more effectively than previous ones, for it includes the results of a vast amount of experience during the recent war, not only in the handling of wounds and fractures, but in the foot complaints which constitute such a large part of military, industrial, and even civilian practice, and which, unfortunately, rarely receive the attention they deserve outside of military circles. The book is so organized that it is a ready source of reference for the busy general practitioner, with the pertinent facts of diagnosis and treatment condensed in table form, a highly effective way of making information easy to obtain. At the same time, the text itself is so detailed and definitive that the book serves equally well the needs of the orthopedic specialist.

Fundamental in understanding and evaluating the many disturbances of the foot and ankle is, of course, a thorough knowledge of anatomy, here described in full and complete detail. But even further, an entire chapter on "Physiology and Bio-Mechanics of the Foot and Ankle" analyzes in detail the many forces and components which operate here, and how distortions of those forces produce many of the common complaints in the lower extremities.

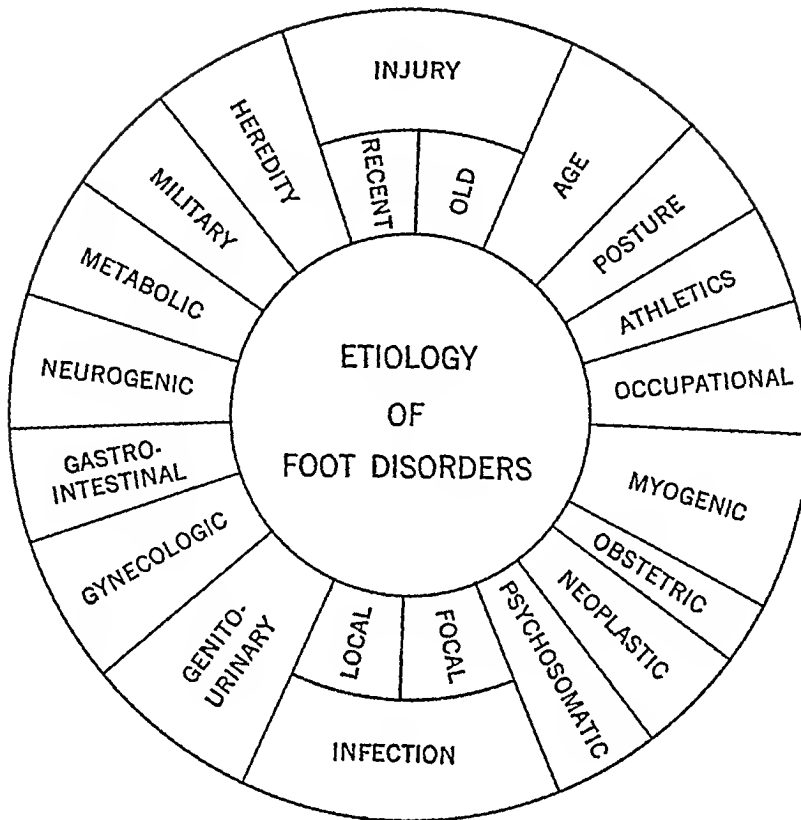
In another way, too, Dr. Lewin's book is out-

*The Foot and Ankle; their injuries, diseases, deformities, and disabilities. Philip Lewin, M.D., F.A.C.S. Third edition, thoroughly revised. Philadelphia, Lea & Febiger, 1947. Price \$11.00.

standing, for it approaches the problems of this limited area not only in relation to the whole body, but to the environment, that is now popularly known as the "psychosomatic approach." Military surgeons saw many, many complaints in this region for which there was no organic basis, and Dr. Lewin takes up in some detail the emotional influences upon the foot and ankle, as well as postural and other relationships of the rest of the body as they affect this region. Perhaps this is the most outstanding contribution of this new edition, for orthopedic writing is too often limited to the bones and joints themselves as purely mechanical problems, with little if any consideration of the personality as a whole. As these relationships become apparent and are properly evaluated, it will be found that this concept is widely applicable, not only in industrial and military practice, but in everyday office routine, where, it is safe to say, few foot complaints receive the expert attention they deserve.

Shoe fitting is the most neglected of arts. Dr. Lewin points out that "In each of the forty-eight states of the union, every blacksmith must have a state license to shoe a horse. In no state is a shoe fitter required to have anything more than a yardstick, a shoe horn, and a glib tongue. It doesn't sound like horse sense, does it?" Fourteen pages of the text are devoted to the shoes and can be studied with profit by general practitioner and specialist alike. "Flat feet," too, the most common complaint in this region, receive thorough and sensible consideration in some thirty pages.

Ample covered also, are the sometimes obscure trophic and circulatory disturbances, such as Sudeck's atrophy, which result in considerable disability, as well as the extremely painful causalgic syndromes that often followed such conditions as



From: Lewin, "The Foot and Ankle"

trench foot, as well as fractures and wounds which were immobilized for long periods. These causal-gias are prolonged, very disabling, and difficult to treat. With the "home town medical care" program of the Veteran's Administration, many physicians will be seeing such conditions for the first time, and Dr. Lewin's discussion forms a valuable basis for understanding and treating them.

Fractures, of course, must be treated thoroughly in any orthopedic text, but Dr. Lewin emphasizes particularly an aspect of ankle region fractures which impressed most military surgeons very forcibly during the past war. This was the high incidence of crippling disability in many fractures, with widening of the ankle joint mortise and instability of the joint. His conclusions—that many of

these fractures should be treated surgically by means of open reduction and some sort of fixation, such as a bolt through the tibia and fibula just above the joint—are amply justified by military experience, and should lead to a closer study of individual cases, rather than the "conservative treatment and wait for results" method now commonly employed.

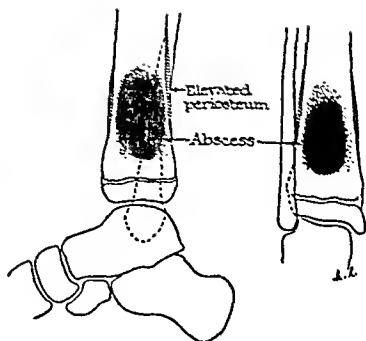
Operative procedures are described fully, as well as the treatment of the difficult "trimalleolar fracture," which so often results in a high degree of disability, if not recognized and reduced properly from the beginning. The point is well taken that operative treatment in these complicated ankle fractures is not complicated and yields a high degree of good results.

TO THE general practitioner who is called upon to treat an occasional industrial accident case, nothing is more difficult than the proper evaluation of disability in these patients, particularly in compensation reports. Chapter XX gives in six concentrated pages a workable and simple method of accomplishing this task. This chapter alone will well be worth the price of the book to anyone facing such problems.

The following chapter on military aspects of the foot and ankle gives a thorough and up-to-date coverage of problems peculiar to the armed services, as well as lessons learned in wound care, which will be invaluable to traumatic surgical practice in the future. A large section of the book is also given over to the treatment of neurologic lesions, both those of psychosomatic origin, and those secondary to other organic disease, including a complete coverage of the orthopedic management of poliomyelitis.

Still another of the significant contributions of war surgery to the traumatic field was the realization that vascular disturbances are extremely important in injuries of the extremities. Nothing was more dramatic than to see pain and swelling around fractures disappear following blocking of the sympathetic supply at the lumbar ganglia. And since the lower extremities seem to be the weak link in the circulatory chain, it is here that symptoms of vascular origin are so frequently seen in orthopedic practice, as well as those from diabetes and other causes.

A large section of the book is devoted to these important circulatory aspects of foot and ankle symptoms, including varicose veins. All of this is, of course, quite in line with the major premise that bone and joint symptoms are often markedly influenced by the general body condition, as well as local tissue changes connected with both innervation and circulation. Dr. Lewin's admonitions to diabetics in regard to care of the feet might well be reprinted and distributed by the general physician to all his diabetic patients.



From: Lewin, "The Foot and Ankle"

Figure 257. Brodie's abscess (chronic osteomyelitis) in the lower third of the tibia. Lateral and anteroposterior views. Drawn from roentgenograms.

Fungus infections were the cause of many foot complaints in military and naval practice. The orthopedist who sees such conditions may refer them to the dermatologist, but the general practitioner will usually have to treat them himself. Patients, and too many doctors, overtreat such infections, as Dr. Lewin points out. His section on this problem and others in the care of the feet are concise and sensible and form a ready reference for the busy physician. Finally, emphasizing again his contention that the feet are parts of the body and their disturbances part of general body disturbances, one of Dr. Lewin's amusing "pedigrams" may be quoted:

*"Little bits of flat feet
Little squeaky knees
Make the Goldthwait sickness
Sacroiliac disease."*

F. G. S.

MEN OF MEDICINE

The "Baby Doctor"

WHEN, a little over eighty years ago, Dr. Isaac Arthur Abt was born to the family of a clothing merchant in Wilmington, Illinois, newborn infants had only about a fifty-fifty chance of survival. As the doctor himself recalls those days, before the term "pediatrician" became a familiar word to parents, "it was almost a tragedy to bring a baby into the world." A family of ten children was considered fortunate if as many as seven survived. Children in the lowlands died of malaria; other young lives were snuffed out by sweeping epidemics of scarlet fever and diphtheria, while many who survived "summer complaint" succumbed to various respiratory diseases in the winter.

At that time there were fewer "baby doctors" in United States than you could count on the fin- of one hand. The general practitioners who care of children treated them with the same medicine that they used for adults; they had very few remedies in their black bags for the more serious ills of childhood. The practice of giving children a different sort of attention from that given adults was not popular among general practitioners, and, of course, parents did not expect it.

Few hospitals in the civilized nations were equipped to care for children; parents generally feared them as places to which their children were taken to die. When Dr. Abt was born, there were a few children's hospitals in Paris; one in London, the Great Ormand Street Hospital; and another in Vienna, which had been organized in the first quarter of the nineteenth century. There was a nursery and a children's hospital in New York City, and a good many of the young doctors were trained in the New York Foundling Asylum. The children's ward of the Cook County Hospital in Chicago was a dismal place where the sick or in-

jured child all too frequently died as a result of such condition.

The situation had changed but little when Dr. Abt became an intern at Chicago's Michael Reese Hospital in 1891. The great discoveries in medicine that nowadays give parents a feeling of security about children's health had yet to be made. It was in the fight to add to these discoveries and to apply them to the science of pediatrics that Dr. Abt has made his contribution, and today he stands at the top among those who heroically labored for these principles.

Though small of stature and slight of build, Dr. Abt had boundless energy that stood him in good stead as he fought against old, outworn methods and popularized among doctors, laymen, and hospital and public authorities the application of the new science. His colleagues say he was at least twenty-five years ahead of his time. The well-appointed hospitals for babies and children, which today may be seen in every large American community; ample milk supplies free from dangerous bacteria; and vaccines, antitoxins, and toxoids, widely applied—all have become a reality through the tireless effort and driving force of leaders such as Dr. Abt and the men who have followed him.

Today Dr. Abt, who likes to consider himself a "baby doctor," can look back on his tempestuous career with a philosophical calm, as he sits in a big easy chair in the study of his apartment on the south side of Chicago and smokes long, black cigars. As he talks, his interest shifts from medicine to poetry, to his love of living creatures on the farm, to the cultivation of plants and animals.

He likes to recall the old days at his home at Wilmington. He and his twin brother were part of a family of five children, and he remembers only too well the times when his brothers and sis-



ISAAC ARTHUR ABT

ters were dangerously ill and how he shared his parents' anxiety as they frequently applied home remedies. His grandmother did most of the doctoring, and always kept ready for any emergency a salve made of beeswax and resin. She prescribed blackberry brandy for diarrhea and Jayne's vermifuge for worms; her cough medicine was compounded of onions, molasses, and vinegar. He told how they cut slippery elm branches and made tea of the bark to give to his brother when he had pneumonia.

His early college days at Johns Hopkins were gay with boyish pranks. The university was young and thriving when he entered in 1886, with some of the nation's leading scientists on the faculty.

He recalled one prank in particular—the time when he and a fellow student, strolling down a street in Baltimore, came upon a crowd of men and women blocking the sidewalk. Pushing their way through the crowd, the two young students saw a man lying on the pavement. It was plain that the man was the victim of an epileptic fit. Both boys immediately assumed a professional attitude. With an air of authority they called over a man with a white apron who had just come out of a restaurant, and ordered him to bring them a sack of salt. He quickly obeyed, and they rubbed the salt on the face of the prostrate man. He recovered immediately, and the boys walked away with great dignity while the people in the crowd gazed at them in admiration and respect.

AFTER finishing three years of schooling at Johns Hopkins, Abt entered the old Chicago Medical College of Northwestern University, then occupying an old, dilapidated building. Many of his fellow students had gone no further than elementary or high school. The laboratories were badly equipped and poorly lighted. The full time teaching staff consisted of one professor, but the lecturers were excellent men. From Dr. Frank Billings the young student learned the importance of doing thorough physical examinations, something Dr. Abt has emphasized throughout his career as a practitioner. Dr. Billings examined his patients in minute detail from the tips of the toes to the crown of the head.

Little, however, was taught about the care and treatment of infants and children. Most of what he learned Dr. Abt picked up from experience, and he accumulated experience rapidly. His internship was a rugged regimen indeed. The demand for medical care among the hospital's clientele kept him on his feet all day. There was little time for sleep after hospital duty late at night, since Dr. Abt often had to be up at seven o'clock in the morning to help in surgical operations. This established the pace that the future baby doctor followed the rest of his career.

Frequently the privilege of being an intern at Michael Reese was not a very dignified one. Orderlies were not always available, and he then had to be his own orderly. But the discriminating supervision of the attending physicians gave him a sound fundamental training in diagnosis and treatment.

As he worked with infants and children, he became increasingly aware of the great vacuum in medical knowledge regarding their ailments. He searched for every source of information that he could scrape together. He studied the work of Abraham Jacobi, J. Lewis Smith, Herman Widerhofer, and a few others who had shown some interest in that neglected field. He tried to discuss with the attending physicians problems of children's diseases that bore heavily on his mind, but found they were not too interested.

Dr. Abt, however, persisted in his interest. When his internship was over, he sought the men in Europe whose work he so avidly read. He went to Vienna and Berlin for postgraduate work, attended Dr. Widerhofer's clinics in St. Annen, and worked under Dr. Adolph Baginsky at the Kaiserin Friederich Spital in Berlin. They had progressed much farther than the physicians in America in treating the ills of infancy and childhood, but even the great Baginsky possessed no satisfactory weapons against the ravages of diphtheria.

The facilities in his native America seemed hopelessly inadequate compared with those in Europe when he returned home the following year. The challenge stimulated his youthful energies, and he eagerly prepared to enter practice. His office was a barren room, heated by a stove, and had no rugs or curtains. His mother, out of her savings, helped

him buy the few pieces of furniture it contained. Then he waited for patients. It was several days before anyone called. The first was a man who brought in a dog that had been prepared for an exhibition; he asked the young baby doctor to fix the dog's tail which had been improperly trimmed. Dr. Abt gave it as much care as he would a human infant. Putting the dog under anesthesia he then retrimmed the tail in best dog show form; he received a fee but never had the satisfaction of knowing whether his surgery helped the animal win a prize. Another of his early patients was a sick canary. He treated it, but it died, and he had the satisfaction of receiving it as a gift for dissection.

But in those days, in a crowded Chicago neighborhood in which there was an overabundance of childhood illness, he did not have to wait long for patients to arrive. Then in 1897 he was named professor of diseases of children in the Women's Medical School at Northwestern, attending physician at the Old People's Home and the Jewish Orphan Asylum, and pediatrician at the Chicago Orphan Asylum.

His varied responsibilities required him practically to cover the town, so his mother bought him a horse and buggy. The horse was old and the buggy rickety, but he traveled in grand style. In 1897 he married Miss Lena Rosenberg, a nurse at Michael Reese. They hired a maid and set up housekeeping; he considered himself to be well established.

ABOUT that time Dr. Abt had the exciting and gratifying experience of being the first doctor in Chicago to test von Behring's newly discovered antitoxin for diphtheria. His reputation for success in the practice of intubation was so wide that doctors frequently sought his help when they had a serious case of diphtheria on their hands. One of his colleagues called just after Dr. Abt had heard that a Chicago druggist had received a shipment of the antitoxin. Answering the summons, Dr. Abt picked up the supply of antitoxin and rushed to the patient's home. The child's skin was blue; his pulse was weak. Dr. Abt administered the antitoxin, and he and his fellow practitioner waited through the night. Gradually the child's color re-

turned, his temperature went down, and he began breathing regularly. In a few days he had recovered completely.

Eagerly Dr. Abt went about publicizing and popularizing his new knowledge, doing everything in his power to wipe out the traditions that hampered the performance of such "miracles." But many a rugged battle was needed to put the new knowledge of bacteria and the avoidance of infections across to the public, the authorities, and hospital people. Between the time that Dr. Abt transferred from Northwestern to the position of associate professor of diseases of children at Rush Medical College in 1902, and back again to Northwestern in 1909 as professor of diseases of children in the medical school, he fought for better hospitals for children, pure milk, better feeding of babies, and a host of other measures that are today directly responsible for the nation's low infant mortality rate.

In that same period Dr. Abt served as a health inspector in the city of Chicago. He acted as a diagnostician of infectious diseases, and administered antitoxin, performed intubations, did vaccinations, and visited schools where health examinations or emergency treatments were required.

At the turn of the century definite progress in the acceptance of newer ideas in pediatrics could be noticed. There was growing interest in the proper feeding of children to prevent gastrointestinal disorders. Baby doctors had started to try a variety of things—the addition of barley water to milk, diluting milk, peptonizing it, and trying to treat cows' milk to make it resemble mothers' milk.

At that time most of the milk consumed in Chicago was infested with bacteria, carrying tubercle bacilli and other disease-bearing organisms. In both the hospital and slum home the milk consumed was uniformly deadly. Assuming the leadership in the fight against this danger, Dr. Abt was named chairman of a newly formed Milk Commission. He proposed pasteurization of milk and inspection of herds, but encountered violent opposition from the city council and other authorities. Despite threats to throw him out of one council meeting, he carried through his attack, and persuaded the council to appropriate money to set up a pasteurizing plant and distributing stations for safe

milk. The crusader made speeches and set up exhibits, not only in Chicago and the surrounding towns but throughout the country. Gradually the tuberculosis death rate and the incidence of typhoid were lowered, and gastrointestinal disease started to decline. By 1915 results of his efforts were definite and striking.

In the midst of his fight to stem the spread of bacterial diseases, Dr. Abt carried on an extended controversy with hospital authorities against the poor accommodations for infants and children. At the turn of the century Chicago had little for which to be proud in the operation of such places. Dr. Abt had visions of well-lit rooms with an abundance of fresh air, glass cubicles to separate patients so the dangers of spreading infection could be minimized, well-planned private rooms, diet kitchens, laundries where all clothing could be kept spotlessly clean, and efficient medical and nursing staffs. His visions were in sharp contrast not only with reality but with the ideas of hospital operations that existed in the minds of superintendents in those days. It was a long struggle to get them to see things his way and his disappointments in this effort were frequent.

DR. ABT says that when he became attending physician at Cook County Hospital in 1900, it reminded him of an old charnel house. On one occasion it was actually that. The ward was filled with sick children when he was called out of the city over the week end. When he returned the children had gone. He asked a nurse where they were; she told him that all of them had died. The children's ward consisted of one room. The older children were kept on the main floor and the younger ones on the balcony that surrounded it. The food was contaminated and unwholesome. There was no protection against spread of disease.

Eventually the authorities were persuaded to build a new children's pavilion. They erected a three-story structure, but with an eye to economy they neglected to install an elevator, so the building had to be torn down within a few years.

In 1910 he received funds from the Nelson Morris family to build the Sarah Morris Hospital for children. He developed plans for the new struc-

ture after visiting some of the outstanding institutions in Europe and in the eastern part of the United States. He finally was able to realize his visions. It was a type of an institution to which parents were no longer afraid to take their children. It became a mecca for pediatricians the country over, and a pattern for children's hospitals in other cities. But the Sarah Morris, which was constructed as a wing to the Michael Reese, fell short of meeting his demands, and he finally resigned as attending physician to accept a similar appointment at St. Luke's, where he served until 1932. He then became a member of the consulting staff of Children's Memorial Hospital. Dr. Abt also served as attending physician for diseases of children at Passavant.

Looking back on those days of progress in the treatment of children's ills, Dr. Abt recalls gathering a rich store of knowledge from students and patients as well as imparting it. He brought his medical students into the hospital and gave them thorough training in close observation, elaborating on the invaluable technics he had acquired when he was a student.

He encouraged discussions, and in many talks with his students he practiced the utmost frankness and willingness to learn himself. If a student questioned a statement he had made, he was willing to be proved wrong. When he found that he lacked sufficient evidence, he would go to his study after school hours and search through medical books and journals until he found a satisfactory affirmation or denial. Dr. Abt also liked to bring his students to his home where they would have prolonged "bull sessions." He would always listen carefully when an intelligent and observant parent or nurse described the symptoms of an ailing child. Such descriptions stimulated his thinking and helped him in diagnosis.

Early in his practice he had learned to handle difficult parents, aunts, uncles, cousins, and neighbors of his patients. He had to combat folklore and old wives' tales and to develop methods to use with hysterical mothers and overprotective parents.

A classic is his advice to one mother which he gave many years ago:

"My baby won't eat his baked potato," the distraught mother called over the telephone. "What

"shall I do?" "Don't let it go to waste," he snapped back. "Eat it yourself."

On another occasion, a mother brought her small daughter into his office. When the woman wasn't wringing her hands she was fondling her pearl necklace. Her daughter wouldn't eat and wouldn't sleep, she complained. "What shall I do?" she asked. "Get a psychiatrist," Dr. Abt replied, "for yourself."

THANKS to the crusading efforts of Dr. Abt and others like him, the knowledge of pediatrics was being developed and applied at an increasing rate. "Lots of young doctors were taking a fancy to the subject," he says, "and were adopting pediatrics as their specialty." In 1912, Dr. Abt embarked on the new project—his now famous *System of Pediatrics*. He accumulated books, journals, and other publications until the floors of his home sagged and the doors stuck. In spite of a large private practice, his responsibilities at several hospitals, and his teaching load, he would come home in the evening "dog-tired" and write until late at night, preparing syllabuses and sending them to doctors all over the country. He had planned to have sections in this exhaustive treatise written by European doctors as well as American, but World War I prevented the fulfillment of this intention. At times when he and Mrs. Abt were invited out for the evening, he would dress for the occasion and return to his desk. He would become so interested in his work that he could not be persuaded to leave it, and Mrs. Abt would have to go out alone. Upon her return she would find him still in his evening dress, continuing his work.

He continued work on his *System of Pediatrics* for years. It finally became a huge work of eight quarto volumes of about 1100 pages each. But in spite of the late hours of work he was always ready at 7:30 in the morning to start his hospital rounds. In fact, it seemed that nothing could stop him. One morning in 1918 he received a call because he left home that the Michael Reese was snow-bound. Snow had piled up so high during the night that it was impossible for anyone to leave or reach the place. He had two automobiles, but when he tried to run them, they stalled. He then

found a horse and an old sleigh in the neighborhood and had them hitched. He drove four miles through drifts and over snowbanks to the marooned hospital.

Dr. Abt reached retirement age at Northwestern in 1938. Although he did not retire from practice, he began to relax and let his mind drift to other activities. His wife had died in 1929. He had always loved the fishing trips he had taken with her and their two sons to northern Michigan for many summers, so in 1933 he bought a 360-acre farm near Traverse City. Characteristic of his thoroughness, he began to accumulate books, journals, and pamphlets on every aspect of farming and read them avidly. He had sent most of his medical library to Northwestern and had moved to the apartment he now occupies alone, with a housekeeper living next door. His supply of agricultural literature almost equaled his previous accumulation of medical books. He visited farms, agricultural experiment stations, colleges, and other institutions wherever he could gather agricultural information.

"It was great fun and a lot of excitement," he relates. He hired others to work the farm, but he would go there whenever he could break away from his responsibilities in Chicago. He indulged himself in the fun and excitement until 1945, when he decided to give it up and settle down to a calmer, more philosophical, and contemplative life.

He reads poetry and finds a great deal of pleasure in the Victorian poets, Longfellow, and Tennyson. He likes Robert Louis Stevenson and reads scholarly studies of the Bible, biographies, and essays. He feels that he has not retired and still maintains an office where he goes for an occasional consultation.

He enjoys receiving friends in his home, including visitors from far and wide who come to pay their respects. He has many pleasant evenings with his two sons, Dr. Arthur F. Abt, a pediatrician, and Lawrence E. Abt, a Chicago merchant, their wives, and his three grandchildren who visit him frequently. He attends medical meetings and recently read a paper at the Chicago Medical Society on the "Comparative Anatomy of the Thyroid Gland" based on studies of a large accumulation of literature.

Last December 18, when Dr. Abt reached the age of 80 and the Northwestern University medical school gave a reception in his honor, the question of his retirement was brought up. "Just when should a man retire?" he asked, but did not offer to reply. He has tried to retire three times. The last time was in 1941, when he took over the practice of his son, who went into service in the Naval Medical Corps.

Dr. Abt believes that as men grow older they unlearn much that they have learned, a process which continues throughout their lives. He thinks that the newer generation of pediatricians is obsessed with laboratory examinations, which take the place of much of the older doctors' thorough observations. "But," he adds, "it is customary for the older generation not to be hospitable to the advances of the newer generation. The older men always have some misgivings as to what the young fellows are up to, but I guess the young fellows are all right."

He believes that the healing art "is one of the sublimest and noblest, in that its obligations are intimately related to the first and noblest principles of religion and love of humanity, and its practice necessitates self-denial and elevation of the sentiments above the common concepts of life." He warns the physician against "making fame and fortune the object of his striving," for he will be in "constant conflict with himself, and his hopes will always be disappointed."

DR. ABT's research achievements have been numerous. He is the author of a long list of monographs. His investigations dealt with floating kidneys in children, acute nonsuppurative encephalitis, rachitic erosions of permanent teeth as a result of infantile diseases (with Mortimer Frank), traumatic diabetes, "starch injuries," unusual types of acid intoxication, chorea, familial icterus in newborn infants, and other subjects.

Dr. Abt is one of three American pediatricians to be elected an honorary member of the Deutsche Gesellschaft für Kinderheilkunde and is Chevalier of the Legion of Honor. He is a former president of the American Pediatric Society, the American Academy of Pediatrics, the Institute of Medicine of Chicago, the Chicago Medical Society, and the American Association of Teachers of Diseases of Children; a member of the American Medical Association, the Chicago Pediatric Society, Central States Pediatric Society, and the Children's Hospital Association of America. He is also an honorary member of the Washington Medical and Surgical Society and of the Minnesota chapter of Alpha Omega Alpha fraternity. He is the author of the book, *The Baby's Food*, and more recently a popular book based on his career, entitled *Baby Doctor*. Besides his editorship of *The System of Pediatrics*, he also edited the *Yearbook of Pediatrics* for many years, a volume on pediatrics in the Practical Medicine Series.

R. A. B.

Foreign Surgeons at Work

REPORT OF A TRIP TO THE INTERNATIONAL SOCIETY OF SURGERY IN LONDON AND THE FRENCH SURGICAL CONGRESS IN PARIS

WALTMAN WALTERS

DIVISION OF SURGERY, MAYO CLINIC, ROCHESTER, MINNESOTA

MY TRIP to London was made to attend the twelfth meeting of the International Society of Surgery (Figure 1). The second week of my trip was spent attending a continuation of the meeting in Edinburgh, the third week was spent in Switzerland, where I visited the clinics of Bruner at Zurich and of Jentzer at Geneva, and four days of the fourth week were spent attending the fiftieth meeting of the French Surgical Congress in Paris.

Six hundred surgeons from all countries except Russia and Germany attended the meeting of the International Society of Surgery. A limited number of these surgeons (100) went on to Edinburgh where clinics and surgical papers were presented for four days. One thousand French speaking surgeons attended the fiftieth meeting of the French Surgical Congress.

I flew with several other American surgeons from New York to London (fifteen hours). I also flew from Edinburgh to London (three hours), from London to Zurich (three hours), from Geneva to Paris (one hour and forty minutes), and returned on the Queen Elizabeth (five days). I left Rochester on September 12, 1947, and I returned on October 18, 1947.

The International Society of Surgery selected the following subjects for consideration by the respective speakers.

"The role of penicillin in surgical practice," by Sir Alexander Fleming (London).

"Recent advances in arteriography and venography," by Professor Dos Santos (Lisbon).

"The surgical treatment of pulmonary stenosis," by Dr. Alfred Blalock (Baltimore).

"The results of early operation in war wounds of the lungs," by Dr. Bastos Ansart (Barcelona).

"Recent progress in the treatment of burns," by a Russian surgeon.

"Recent advances in surgery due to heparin," by Dr. Crafoord (Stockholm).

"Skin defects; their repair by flaps and free skin grafts," by Professor T. Pomfret Kilner (Oxford).

The Russian surgeon was the only one of the principal speakers who was unable to attend the meeting.

Each of the principal speakers was given thirty minutes for his presentation. All members of the Society who anticipated attending the meeting were notified to make application to discuss various papers. Such discussions were limited to five minutes. I requested permission to discuss the papers on penicillin and heparin.

During the entire week of the meeting in London, surgical clinics were held in the different hospitals. I visited Guy's Hospital to see Dr. Blalock perform an anastomosis between the subclavian artery and pulmonary vein (Figure 2) and to see Sir Heneage Ogilvie do a partial gastrectomy. The Royal Free Cancer Hospital was visited to see Dr. Abel do some operations on the colon and also to see the type of research that is being done on cancer at that hospital. I visited Middlesex Hospital to see Mr. Riches do some urologic operations. I was particularly anxious to see him perform the retropubic prostatectomy of Millin. This operation should be performed more frequently in the United States than it has been in the past. The mortality associated with this operation is as low as that associated with transurethral resection. The adenomatous lesion seldom recurs after a retropubic prostatectomy has been performed. I also visited the Waterloo Hospital and the South End General Hospital* in order to see Mr. Rodney Maingot do some gastric operations.

During this week of the meeting, either a reception or a dinner was given each day by the officers of the Society or by officers of the Royal Society of Medicine and by Mr. Bevan, Minister of Health for His Majesty's Government.

The surgical technic that is used in England varies only slightly from that used customarily in the United States. The judgment of the surgeons was excellent and the operations were performed skillfully. In the London hospitals I visited blue and green linens are used in the operating rooms. These colored linens are

*This hospital is situated at South End by the Sea, which is a beautiful small community at the mouth of the Thames, an hour and a half by train from London.

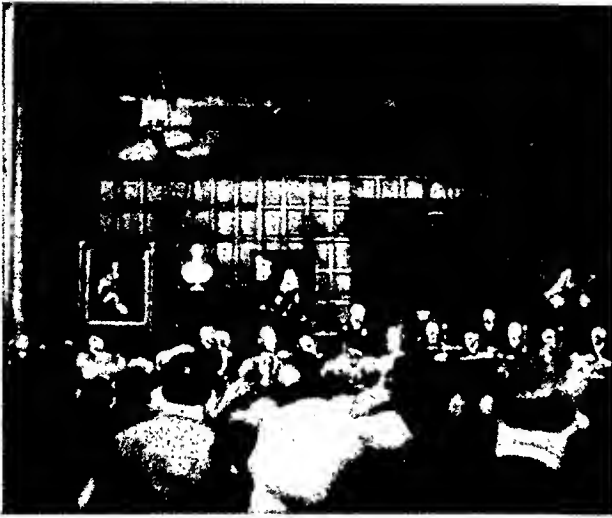


Figure 1. Mr. Grey Turner speaking at the inaugural session of the twelfth meeting of the International Society of Surgery in London.



Figure 2. Dr. Blalock operating at Guy's Hospital.

more restful to the eye than is white linen and they do not show blood as readily. Color used in curtains, draperies and bedspreads, and in patients' rooms and the wards created a feeling of warmth and a homelike atmosphere which was very pleasing.

Attendance at the social functions was a very important part of the meeting, because it gave one an opportunity to visit with men from different countries and to discuss surgical problems. This frequently is impossible at medical meetings because persons are difficult to find in the crowd.

In the week after the meeting, the Royal College of Surgeons conferred honorary fellowships on Dr. Arthur Allen (President of the American College of Surgeons), Dr. Abel (past President of the American College of Surgeons), Dr. Blalock, Dr. Evarts Graham, Dr. William Gallie (Toronto), Dr. Frank H. Lahey and Dr. Dallas B. Phemister. Dr. Gallie was given the gold medal, which has been presented only twenty times in one hundred forty-seven years. Dr. Graham was given the Lister medal.

Dr. Arthur Allen as President of the American College of Surgeons presented a beautifully carved oak table and lectern to the Royal College of Surgeons in appreciation of the gift of a mace from the Royal College of Surgeons to the American College of Surgeons several years ago. It is also interesting to note that the American College of Surgeons gave \$40,000 to the Royal College of Surgeons of England to assist in the restoration of the bombed-out portions of the Royal College of Surgeons' building, which was practically completed at the time of the meeting. Figure 3 shows the results of the bombing in the vicinity of Guy's Hospital.

IN THE week after the meeting in London, a hundred members of the society went to Edinburgh to attend a continuation of the meeting (Figure 4). Professor Learmonth (Figure 5) had arranged an excellent program of operations and lectures. The surgical work was excellent and the reports of the clinical and experimental investigations were of the highest order. All of the members of the society were loud in their praise of the excellent work which was being done at the University of Edinburgh and of the excellent and coordinated program which Professor Learmonth had arranged.

In Edinburgh, as in London, either a reception, a luncheon, or a dinner was held each day. In making inquiry about how the food was procured for the receptions and dinners in both Edinburgh and London, I found that the surgeons and their families contributed many of their own food rationing points so that sufficient food could be made available for their guests during the meetings.

In Zurich I spent one morning making rounds with Professor Bruner at the University Hospital. Since Monday morning was given over to making ward rounds, I saw practically all types of cases on the surgical services of Professor Bruner and his associates. He has seventeen assistants including four Oberärzte who act in the same capacity as associate surgeons, that is, they operate independently, but under the direction of the professor.

Professor Bruner is one of the best known thoracic surgeons in Europe. At the University Hospital, in addition to his wards for general surgical cases, he has been assigned two pavilions of fourteen beds each for patients who undergo operations for pulmonary tuber-

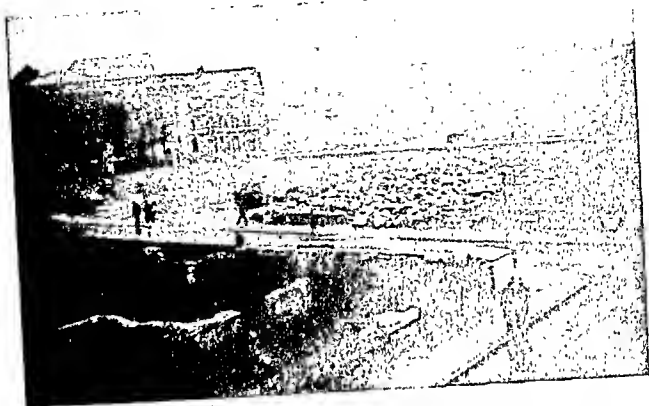


Figure 3. Results of enemy bombing around Guy's Hospital.

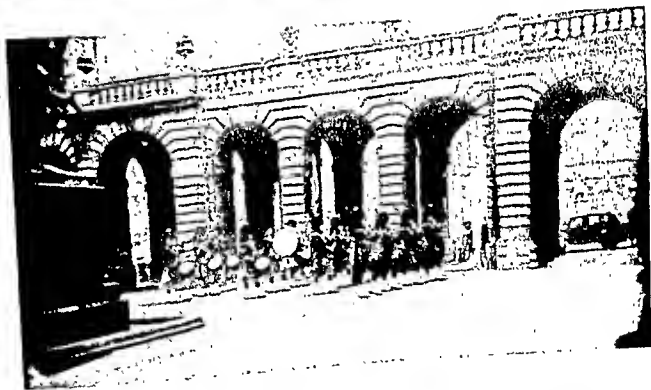


Figure 4. Police bagpipe band in front of the City Hall in Edinburgh, at the reception given by the Lord Mayor for the members of the International Society of Surgery.

culosis. Practically all of the European hospitals are of the pavilion type.

In Geneva, I spent one morning in the surgical clinic of Professor Jentzer where I watched him perform four operations in three hours in one operating room. These operations included the removal of a subdural hematoma, two operations on the stomach, and a nephropexy. All the operations were well done; team work in the operating room was excellent.

AT THE fiftieth meeting of the French Surgical Congress, which was held in Paris, the following subjects were considered: (1) painful lesions of the am-

putated extremities, and (2) dystrophies of the biliary tract. The principal speakers and the discussors had been selected by the program committee. Dr. Richard Sweet (Boston), Dr. A. Earl Walker (Baltimore), Dr. John H. Garlock (New York) and I were the American surgeons who participated in the program. I had been asked to discuss Poilleux and Guillet's paper on biliary dystrophies. I based my discussion on a continuation of studies on the pathologic physiology of the common bile duct. The original study was reported by McGowan, Buch and me several years ago. I used a motion picture and cholangiograms in my discussion. I had a French surgeon, Paul Banzet, translate the legends into French and

read them after I read a short French translation summarizing the paper. Studies of the function of the biliary ducts by measuring intraductal pressures and cholangiography have been of particular interest to French physicians and surgeons.

While I was visiting the surgical clinic of Dr. Bergeret at L'Hopital Antoine, I saw a unique operating table that had been constructed so as to permit roentgenoscopic studies of the biliary tree to be made by a technician while lying in a darkened enclosure beneath the operating table. Films are exposed during various phases of the study, are passed through a slot at the end of the operating table, and are taken across the operating room and passed into another slot which brings them to a dark room adjacent to the operating room. They are developed immediately and they then are viewed through a frosted screen in the door between the operating room and the dark room. This is a very ingenious arrangement.

With the exception of an invitational dinner, practically no social functions were held in conjunction with the French Surgical Congress. Dr. and Mrs. Blalock, Dr. Edwin Ramsdell (White Plains, N.Y.) and Mrs. Walters and I were guests of the Association at this dinner.

The visible nutritional state of the British, Scotch and French people appears to be no different from that of the Americans. This is true of the people seen on the street as well as of patients seen in the hospitals. The monotony of the diet, however, is beginning to become very tiresome. These people have no white bread, practically no meat, and no eggs. They have little coffee, of a poor grade, and tea is rationed. They have no cream, very little sugar, and a small amount of milk of the poorest quality.

The cost of hotel accommodations in England and Scotland is about the same as it is in the United States but the price of meals is about 33 per cent higher, which increases to 100 per cent if wines or liquor are drunk with the meals. In Switzerland, hotel accommodations and food are good, the equal of those obtainable in all restaurants in the average city in the United States and the prices are reasonable. In Paris, although the price of hotel rooms is about the same as that of comparable rooms in American hotels, the price of food was from 100 to 200 per cent higher than it is in the United States.

ATTENDANCE at an international surgical meeting is a very worth while, not only for members of a particular society but also for visitors who may attend the meeting. It affords members of the society an opportunity to present the results of their own work to surgeons from all parts of the world. It also affords an opportunity for the discussion of surgical problems with surgeons from other countries. In addition, one can see outstanding surgeons operate on patients who



Figure 5. Professor James Learmonth in front of the Anatomy building of the University of Edinburgh.

have lesions of special interest. In spending one week at such an international meeting, one can learn more than he possibly could by taking an independent clinical trip which would require several weeks.

I have crossed both the Atlantic and Pacific oceans by air. Transoceanic travel saves time and is relatively safe. I can recommend this method of travel to physicians or surgeons who are crossing the Atlantic in an easterly or westerly direction, particularly for the easterly crossing. Returning to the United States on a transatlantic liner gives one an excellent chance to obtain a well-earned rest after a strenuous trip. Owing to the difference in foreign customs and languages, a conscientious physician or surgeon who visits foreign clinics or attends foreign meetings will work just as hard, if not harder, than he would if he were doing his usual work in his hospital, clinic, or medical school.

From the standpoint of what I was able to learn and accomplish, I feel that my trip was very much worth while. The members of my family had sufficient food to eat and none of us lost weight. The hotel accommodations were very comfortable and we had no unfortunate experiences to mar our trip.



EDITORIALS

VAGOTOMY VERSUS GASTRIC RESECTION

AT LEAST 85 per cent of the patients with duodenal ulcer make satisfactory progress on medical management, and do not require surgical intervention. The controversial question today is what is the treatment of choice for those patients with complicated duodenal ulcer who require operation. Some believe that radical gastric resection is the treatment of choice, whereas others prefer the more conservative procedure of vagotomy combined with pyloroplasty or gastroenterostomy.

An operative mortality rate of 2.1 per cent following subtotal gastrectomy for duodenal ulcer has been cited as evidence favoring this procedure. But even a single death incurred in the treatment of a disease which does not directly threaten the life of the patient is an irreparable tragedy. Furthermore, even though the mortality rate following gastric resection is relatively low, little has been said of the frequent and incapacitating symptoms which frequently attend radical resections of the stomach. Transabdominal vagotomy, therefore, should be welcomed as a procedure which promises to entail less risk and which, over a period of more than four years, has afforded excellent protection against recurrence of ulcer.

Dragstedt has performed approximately 300 transabdominal vagotomies with "no deaths attributable to the procedure." Most of the reported complications and deaths have followed transthoracic vagotomy, an operation which Dragstedt and many others have abandoned because the stomach can nearly always be denervated as well by the transabdominal approach.

The period of observation has been too short to permit final evaluation of the method. Nevertheless, it is already apparent to some that, at least in the first two years after operation, a properly performed vagotomy accompanied by gastroenterostomy or pyloroplasty is (1) safer than gastric resection, (2) more effective than gastric resection in controlling recurrent ulceration, and (3) preferable to gastric resection because its morbidity is lower and it is more effective in restoring the patient to health and normal activity.

The course of 50 consecutive patients during the first year following gastric resection for duodenal ulcer has been analyzed and compared with that of 50 consecutive patients subjected to vagotomy alone or combined with gastroenterostomy or pyloroplasty. Even if the mortality which for vagotomy was less than half as high as for gastric resection is disregarded, vagotomy has a clear margin of superiority over gastric resection. Eighty-eight per cent of the patients subjected to vagotomy combined with pyloroplasty or gastroenterostomy obtained an excellent result as compared to only 58 per cent of those who were subjected to gastric resection.

Vagotomy has been criticized because of the gastric retention which follows denervation of the stomach. This complication can be avoided if pyloroplasty or gastroenterostomy is employed routinely to facilitate emptying of the paralyzed stomach.

Even those who most strongly oppose the use of vagotomy in the treatment of ulcer do so because they fear that vagotomy will not afford permanent protection against recurrent ulceration rather than because they fear the

end results of sectioning the vagus nerve. They combine vagotomy with gastric resection in the treatment of duodenal ulcer and in so doing accept the additional hazard of resection. This is in spite of the experience of Dragstedt, who has performed vagotomy alone or with gastroenterostomy and has followed his patients for four years without observing recurrences in patients whose stomachs have been denervated.

Gastric resection doubtless will continue to have a place in the treatment of selected cases of duodenal ulcer in which anatomic anomalies of the vagus nerve render it impossible to obtain a satisfactory denervation of the stomach. As the surgeon's experience with vagotomy increases so does his ability to recognize, at the time of operation, whether or not the denervation has been complete. When in doubt, resection of the stomach will add to the risk of the operation but will make control of the ulcer more certain.

G. C.

WHITHER MEDICAL SPECIALISM?

SPECIALIZATION in medical practice is here to stay. As James B. Herrick¹ pointed out twenty years ago and as Johnson² has recently re-emphasized, relationships between the general practitioner and the medical specialist are now fraught with problems many of which are yet unresolved. Certainly in recent years the standards of specialized practice have been greatly improved by the activities of the American Boards. The desirable effects of those operations have been accompanied by the development of new and largely unexpected complications.

Now it seems timely to bring up for discussion the present trends of medical specialism and their implications. Where are the present policies in regard to selection of specialists leading? Are the probable effects entirely favorable to the overall interests and needs of the public and the medical profession?

Several other pertinent questions have not been thoroughly discussed. Will present trends produce too many or too few specialists: For

example, is there a likelihood of having too many surgeons and too few anesthesiologists? Also will the present urge to specialize produce too few general practitioners in relation to the number of specialists? These are questions of profound importance, especially because of the needs of many areas, notably rural ones, for general practitioners, which same areas are in many instances unable to support a group of specialists but should not be deprived of such services. A corollary question relates to the possibility of exacerbating a maldistribution of physicians, especially because of the relatively great need of some rural areas for improved medical services.

The requirements for certification by the American Boards vary somewhat but average four to five years after graduation from a medical school. This lengthy period of special training eliminates for all practical purposes the possibility that younger physicians might carry on a general practice for a few years after their internship before embarking on specialized training—the very suggestion made by Herrick years ago. This is in addition to the well known disadvantages of too early specialization.

Does certification of specialists require too much conformity in the prescribed type of training? The emphasis of present training requirements certainly seems to be much more on the accumulation of established medical and clinical knowledge rather than on the quality or quantity of original work performed or on the recognition of deficiencies of present medical knowledge. Since the time involved in attaining specialized training is at least equivalent to that required for the Ph.D. degree in universities, it might be to the advantage of medical progress to give increased emphasis to the importance of original investigation in medical science.

A related question deals with the rigidity of requirements for specialization. Some physicians should be able to qualify themselves more rapidly than others. Furthermore, the development of rigid requirements tends toward the establishment of a group of examiners who may view the original thinker or the slightly unorthodox approach with misgivings and who

conceivably might reject a candidate with outstanding ability. The possibility of developments within certifying boards along these lines may be, and no doubt is, resisted, but the tendency of any organization constituted and perpetuated as are the American Boards presents this hazard unless steps are taken to avoid it.

The ambition of an increasingly large proportion of younger physicians toward specialty practice is enormously stimulated by recent trends tending to increase the opportunities available to specialists and to restrict those for physicians who have not been certified by an American Board. When government agencies, medical schools and hospitals, for example, either limit the number of non-specialists to whom they will give appointments or make all of the more attractive appointments from the ranks of the specialists, the pressure to become a member of the eligible group is naturally great. This trend is now clearly in evidence.

Before it proceeds much further it is desirable to reach some conclusion as to the ultimate results of the policy and the effects which it would have not only on the institutions concerned, but on the future of medical progress.

The trend of medical practice in this country is closely bound up with the future of medical specialism. The purpose of the American Boards is to improve the quality of specialized practice and this objective is being accomplished. Concurrently, however, a dilemma has developed which is well worth study and discussion. In its constant efforts to supply and improve medical service the medical profession cannot afford to ignore the implications of present tendencies in specialism.

1. HERRICK, JAMES B.: The clinician of the future. J.A.M.A. 86:1-6 (January 2) 1926.
2. JOHNSON, WINGATE M.: Will the family doctor survive? J.A.M.A. 132:1-4 (September 7) 1946.

E. P. J.

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This Month in Medicine

ANNUAL MASS RADIOGRAPHY

Most physicians are agreed as to the value of periodic radiographic re-examination of factory and similar groups. The question which has been asked repeatedly is, "How often should personnel be re-examined?" Some investigators believe that three-monthly checks are essential; others maintain that an annual examination is sufficient. Dick, who recently reported his findings in surveys of English industrial workers, suggests that the annual check is practical and probably sufficient.

This investigator made his first survey in 1944, and made repeated surveys on three successive years. The number of tuberculous persons detected in the first survey was two or three times that found in the later years. Thus 0.8 per cent of 2,912 workers examined in 1944 either had tuberculosis or suspicious lesions; the percentage had dropped to 0.3 per cent by 1947.

This drop in positive cases Dick attributed to the fact that early removal of the infective case greatly lessens the chances of the diseased person's contacts contracting the disease. The infector pool is greatly diminished. Furthermore, the victim of tuberculosis often is detected by mass radiography before he is discharging bacteria in appreciable quantities.

SUGGESTED READING

DICK, W. P.: The yearly re-examination of a factory group by mass miniature radiography. *Brit. M. J.* 1:689 (April 10) 1948.

INACTIVATION OF HEPATITIS VIRUS

THE widespread administration of whole blood and blood fractions to Armed Forces personnel resulted in many thousands of cases of homologous serum hepatitis. The virus derived from the blood of a single victim of the disease could contaminate the blood derived from hundreds of normal persons, when the bloods were mixed at

the plasma collecting pools. This has been a source of grave concern to the various agencies and individuals responsible for the operation of Blood Banks and affiliated organizations.

Several methods have been suggested whereby the blood or blood substitutes can be rid of the virus. Recently, Gellis and his associates have demonstrated that the virus, when mixed with normal serum albumin, can be killed by heat without materially altering the albumin.

Three groups of human volunteers were inoculated with mixtures of icterogenic plasma and human serum albumin solution. One of the 3 groups, composed of 5 men, received the mixture unheated. A second group of 5 men received the mixture after it had been heated for 10 hours at 60° C; the third group received the mixture after it had been heated ten hours at 64° C. Three of the 5 men who received the unheated mixture developed hepatitis. None of the other two groups developed it.

This experiment, combined with other studies of the chemical and physical properties of albumin, establish heating at 60° C. for ten hours as a routine step in the preparation of human albumin solutions.

SUGGESTED READING

GELLIS, S. S., ET AL.: Chemical, clinical, and immunological studies on the products of human plasma fractionation. XXXVI. Inactivation of the virus of homologous serum hepatitis in solutions of normal human serum albumin by means of heat. *J. Clin. Investigation* 27:239 (March) 1948.

LEPROSY

THE chaulmoogrates and the sulfones probably complement one another in destroying lepra bacilli. In a recent commentary on the chemotherapy of leprosy, Sir Leonard Rogers points out that the salutary action of the chaulmoogrates depends upon their ability to destroy vast numbers of lepra bacilli in leprous nodules and lesions. These drugs are especially effective when pushed or when administered intravenously. Under these

circumstances, however, there is a substantial risk that bacilli that survive this treatment may pass from the softened lesions into the blood stream, and produce new lesions at distant foci.

Sulfones prevent this. These drugs act slowly in destroying bacilli in the lesions, but destroy them readily in the blood stream. Hence, the sulfones counteract unfavorable reactions that may result from pushing the chaulmoogrates.

Sir Leonard concludes, therefore, that the combined use of these two classes of drugs should provide the most effective, rapid, and inexpensive treatment of leprosy.

SUGGESTED READING

ROGERS, SIR LEONARD: Combined chaulmoograte and sulphone treatment of leprosy and tuberculosis. *Lancet* 1:515 (April 3) 1948.

RELAXATION IN CHILDREN

DAVISON has found "myanesin" [alpha, beta: dihydroxy-gamma-(2-methyl-phenoxy)-propane], a new British drug, a desirable relaxant for children.

This investigator claims that existing drugs or methods are not as satisfactory as relaxants in anesthesia as is the new compound. Either they do not effect the desired relaxation, or their use involves serious perils.

Myanesin was administered to 44 children between the ages of 24 days and 4½ years. Some of the patients were in serious physical condition. In all, relaxation was good and usually of sufficient duration to render a second dose unnecessary. Ether was used as the anesthetic. There were no deaths or postoperative complications attributable to the myanesin.

SUGGESTED READING

DAVISON, W. H. A.: "Myanesin" as a relaxant in children. *Brit. M. J.* 1:544 (March 20) 1948.

CYTOLOGY AND GASTRIC CARCINOMA

As pathologists become more familiar with cytologic technics in diagnosis of malignancies, these technics should produce more accurate re-

sults. Further, they will be applied to the diagnosis of malignancies in body regions other than the female genital system, for which they were devised. Recently, Graham and her associates have studied the use of cytologic methods as an aid in the diagnosis of gastric carcinoma. Fifty patients with gastric symptoms were studied.

In this group of patients, only 24 had carcinoma. Of these, the cytological technic detected only 15. Manifestly, this is a large error. However, in the series of 24 cases, 7 were resectable; cytological technic detected 5 of the 7 resectable cases. Hence, the technic appears to be more accurate when early lesions are involved. This is because active, healthy, malignant cells are shed in abundance from the surface of early lesions; while in advanced tumors with ulceration and necrosis, only occasional recognizable cells are desquamated. At least, that is the explanation advanced by Graham and her associates. If it is actually the case, it is quite an important observation; because cure of gastric cancer is largely dependent upon a surgical attack during early stages of development. Yet detection of early gastric cancer has been well nigh impossible by existing methods. It is conceivable, therefore, that the cytologic examination of gastric fluids may become a valuable method in the early diagnosis of gastric cancer.

SUGGESTED READING

GRAHAM, RUTH, ET AL.: The cytologic method as an aid in the diagnosis of gastric carcinoma. *Surg., Gynec. and Obst.* 86:257 (March) 1948.

ANTIDOTE TO VITAMIN D

VITAMIN D in large doses has been widely used in the treatment of lupus vulgaris; and it has been promoted by drug manufacturers as a useful therapeutic agent in arthritis. In either disease the optimal dosage appears usually to be near if not beyond the limit of tolerance. Hence, the antidote suggested by Charpy and Pichot is of interest.

These investigators reasoned that vitamin D activates phosphatase; hence they sought substances that inhibit alkaline phosphatase. Cysteine and glutathione were tried and found to be effective. For several weeks, they administered large

overdoses of vitamin D to 3 patients with hopelessly advanced pulmonary tuberculosis, and at the same time injected 1 mg. of cysteine daily.

The blood levels of calcium, cholesterol, and urea remained within their former limits; no signs characteristic of vitamin D intoxication appeared. To 3 other patients with lupus vulgaris, normal therapeutic doses of vitamin D were administered with cysteine. The cysteine appeared to inhibit both toxic and therapeutic effects of the vitamin.

SUGGESTED READING

EDITORIAL: Antidote to calciferol. *Lancet* 1:453 (March 20) 1948. Original article by Charpy and Pichot in *Compt. rend. Soc. de biol.* 141:929, 1947.

TOOTH EROSION BY FRUIT JUICES

CONSIDERABLE research is in progress regarding the erosive action of citrus fruit juices on the teeth. Much of this doubtless has been stimulated by the finding that lemon juice caused serious dental lesions, when consumed in accordance with the recommendations of people who sell lemons.

Recently, Wynn and Haldi have reported the results of their studies on the erosive action of several different fruit juices on the lower molar teeth of albino rats. The animals ingested daily, over a period of 100 days, the juice of apple, grape, orange, tomato, grapefruit, pineapple, or prune. The animals that had ingested the apple, grape, and grapefruit juices had the greatest amount of dental erosion. Tomato juice and prune juice produced the least erosion.

In general, the degree of tooth erosion appeared to be related to the degree of acidity. However, the correlation was not statistically convincing.

SUGGESTED READING

WYNN, W., and HALDI, J.: The erosive action of various fruit juices on the lower molar teeth of the albino rat. *J. Nutrition* 35:489 (April 10) 1948.

DIPHTHERIA CARRIERS

BETWEEN 1 per cent and 5 per cent of the normal population harbor virulent diphtheria organisms. When an acute case of the disease appears in

a community, the incidence has been found to rise to as high as 83 per cent.

Although penicillin is known to be effective against *Corynebacterium diphtheriae*, it has not been widely used in the treatment of diphtheria carriers. The reason is that in the carrier state the organisms do not penetrate the mucous membrane as do the hemolytic streptococci but remain on the surface of the membranes of the nose and throat. Hence, they are not affected by parenterally administered penicillin. With the development of penicillin lozenges, however, the physician is given a most simple means of eliminating the carrier condition.

A recent study of this problem has been reported by Levy. During and following a minor outbreak of diphtheria among patients and employees of a State Hospital in Illinois, 3 carriers of virulent *C. diphtheriae* were treated locally with penicillin lozenges and one was treated with penicillin spray. Lozenges containing 1,000 units of penicillin were given every two hours for six days.

The treatment destroyed the diphtheria organisms within one week. Patients remained free of virulent organisms for a minimum of one year following the treatment.

SUGGESTED READING

KOCHER, R. A., and SIEMSEN, W.: Diphtheria carriers treated with penicillin. *Ann. Int. Med.* 24:883, 1946.

LEVY, A. J.: Local treatment of carriers of virulent diphtheria with penicillin. *J.A.M.A.* 136:855 (March 27) 1948.

EPINEPHRINE SPRAY

ORAL epinephrine spray, if used injudiciously in the treatment of asthma, may cause death. Benson and Perlman of the University of Oregon Medical School have completed a ten-year survey of 2,236 asthmatic patients. Of 648 that used oral epinephrine spray, 48, or 7.4 per cent, have died as a result of having used the spray. Death was attributed to destruction, by the drug, of cells that line the air spaces of the lungs. Plugs of tissue formed in the bronchii and bronchioles, leading to anoxia.

SUGGESTED READING

NEWS ITEM: Injudicious use of epinephrine spray may cause death in asthma patients. *Drug Trade News* 23:47 (April 19) 1948.

R. W. C.

Consultation Service

This special consultation information service is offered as a regular monthly feature of *Postgraduate Medicine*. Readers are invited to call on this Service for answers to difficult medical problems from members of our Editorial Board best qualified to help. Each question will be answered by mail and those of general interest will be published each month. Address all communications to Consultation Service, *Postgraduate Medicine*, 516 Essex Building, Minneapolis 2, Minnesota.

COMPRESSED AIR INJURY

QUESTION: Please discuss "Compressed Air Injury (Rupture of Large Intestine)" due to "jokingly" inserting into the rectum a hose carrying air under approximately 100-pound pressure with release of compressed air.

Points of particular interest are: (1) present mortality utilizing surgical repair within eight hours plus 100,000 units of penicillin and streptomycin 0.250 gm. a.a.q. 3 h.; (2) usual location of injury; (3) incidence of multiple significant lesions; (4) importance and indications for drainage, when streptomycin, penicillin, and sulfonamides are available and exhibited in adequate (please discuss) dosage, and (5) medico-legal aspects when patient is "officially" working, but "accident" (of course) is not in "line of duty," but results from a damnable joke executed by fellow workers.

Your discussion of this increasingly important injury will be sincerely appreciated.

M.D.—Indiana

ANSWER: The first report of a case of rupture of the bowel produced by the introduction of air into the rectum was made by Stone¹ in 1924. Probably a little less than a hundred similar instances have been reported since then.

Some interesting facts have been learned by experiments performed on postmortem specimens. For example, pressure of only about 4 pounds per square inch will produce rupture of the bowel when air is introduced by way of the rectum. The perforation usually occurs singly and in the sigmoidal portion of the colon. Multiple splits have been reported in about 25 per cent of cases. The rent occurs most frequently in that portion of the colon which is covered by the longitudinal muscle bands. The mortality rate, as nearly as one can estimate it, is about 50 per cent. One very interesting fact is that in the case of those patients on whom operation has

been performed within six hours after the injury, the mortality rate is very low. In fact, Lapp² reported 17 cases which he collected, in which operation was performed within six hours and none of the patients died. An estimate of the mortality rate in the case of those patients who received no surgical treatment is about 80 per cent. The average age of patients was about 24 years, and the size of the rent in the bowel varied from a perforation which was scarcely visible to a split about 15 cm. long.

Treatment should be directed toward the control of peritonitis. The following plan should be efficacious. Plasma should be administered immediately after the operation and blood should be transfused during the postoperative period; penicillin should be given daily until it is no longer considered necessary. Lapp gave his patient 100,000 units daily. Obviously, proctoclysis should not be utilized but instead, fluids can be administered by hypodermoclysis. If it is desired, the solution for hypodermoclysis can contain about 0.8 per cent of sodium sulfathiazole, and about 1,500 cc. can be given daily for several days. Swenson and Harkins³ found this useful in caring for their patient.

Your inquirer has asked about medicolegal aspects. It would be advisable for him to discuss the matter with his lawyer friends. Probably some responsibility should rest upon the shoulders of the employer, although the accident usually occurs after the blowing of the whistle for "knocking off." It is conceivable that the company could be blamed for not posting a sign indicating the danger of using the air blast playfully.

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New Drugs

Information published in this department has been supplied by the manufacturers of the products described

ISUPREL

PURPOSE: Potent bronchodilator for inhalation.

COMPOSITION: Isuprel hydrochloride is 1-(3',4'-dihydroxy-phenyl)-2-isopropylaminoethanol hydrochloride. It is a stable, synthetic sympathomimetic amine chemically related to epinephrine. Isuprel is identical with the compound known in Europe as "Aludrin."

INDICATIONS FOR USE: For the symptomatic relief of bronchial spasm. Subjective relief of bronchial spasm is almost immediate, accompanied by a significant increase in vital capacity readings. Often of particular value in the treatment of epinephrine-fast patients.

DOSAGE AND ADMINISTRATION: Administered by oral inhalation either by means of a hand nebulizer or by oxygen-aerosolization. Usual dosage by hand nebulizer is from 5 to 15 inhalations; by oxygen-aerosolization 4 liters of oxygen are used per minute over a fifteen- to twenty-minute period. A total amount of 0.5 cc. should not be exceeded at any one treatment. In the average case, treatment by either method need not be repeated oftener than every four hours. In severe cases, more frequent medication may be necessary.

CAUTION: Isuprel hydrochloride should not be administered along with epinephrine as both drugs are direct cardiac stimulants and may cause excessive tachycardia. They may, however, be alternated if desired. Dosage must be carefully adjusted in patients with hyperthyroidism, acute coronary disease, cardiac asthma, limited cardiac reserve, and in individuals sensitive to sympathomimetic amines, since overdosage may result in tachycardia, palpitation, nausea, headache, or epinephrine-like side effects.

HOW SUPPLIED: Solution 1:200, bottles of 5 cc.

PRODUCER: Winthrop-Stearns, Inc., New York 13, N. Y.

NEOHETRAMINE

PURPOSE: Brand of thonzylamine hydrochloride for control of the active symptoms of allergy.

COMPOSITION: N, N-dimethyl-N'-p-methoxybenzyl-N'-(2-pyrimidyl) ethylenediamine monohydrochloride.

DESCRIPTION: A synthetic antihistaminic (white, crystalline compound which melts at 173°C.; highly soluble and relatively stable in aqueous solution). Rarely produces side effects.

INDICATIONS FOR USE: Relieves hay fever, vasomotor

rhinitis, urticaria, allergic dermatitis, drug sensitivities, and other allergies.

DOSAGE AND ADMINISTRATION: Average individual dose 50 to 100 mg. two to four times (100 to 400 mg.) daily. For mild cases as little as 50 mg. daily. May be safely given in larger, more frequent doses when allergens are present in greater concentration. Tablets to be swallowed whole, or crushed and mixed with jelly or other food and followed immediately by water, milk, or other liquid.

CAUTION: Pending further investigation, use of Neo-hetramine should not be prolonged more than three months.

HOW SUPPLIED: Tablets of 25, 50, and 100 mg.; bottles of 100 and 1,000.

PRODUCER: Nepera Chemical Co., distributed by Wyeth, Incorporated, Philadelphia 3, Pa.

BETA-CONCEMIN ELIXIR—TABLETS

PURPOSE: Supplies all factors of the vitamin B complex; antineuritic; pellagra-preventive; aids in intestinal absorption and assimilation.

COMPOSITION:

	One Teaspoonful Elixir	One Tablet
Thiamine hydrochloride (Vitamin B ₁)	4.0 mg.	4.0 mg.
Riboflavin (Vitamin B ₂)	2.0 mg.	2.0 mg.
Niacinamide	10.0 mg.	10.0 mg.
Pyridoxine hydrochloride (Vitamin B ₆)	1.0 mg.	1.0 mg.
Choline dihydrogen citrate	12.5 mg.	12.5 mg.
Liver, B complex fraction	500.0 mg.	125.0 mg.

INDICATIONS FOR USE: As prophylaxis and treatment of deficiencies of the vitamin B complex. As supplement to the diet in anorexia, malnutrition, restricted growth, anemic and debilitated condition during pregnancy, lactation, infancy, childhood, and convalescence.

DOSAGE: Average adult dose 2 or 3 teaspoonfuls Elixir Beta-Concemin or 2 or 3 Beta-Concemin tablets daily. Children, proportionately less.

HOW SUPPLIED: Elixir Beta-Concemin, 4-ounce, 12-ounce, and gallon bottles. Beta-Concemin tablets, bottles of 100 and 1,000.

PRODUCER: The Wm. S. Merrell Company, Cincinnati, Ohio.

WHITE'S MOL-IRON LIQUID

PURPOSE: Treatment of iron deficiencies.

COMPOSITION: Each teaspoonful (4 cc.) contains 195 mg. (3 gr.) of ferrous sulfate and 3 mg. (1/20 gr.) of molybdenum oxide.

INDICATIONS FOR USE: Particularly well adapted to treatment of hypochromic anemias in infants and children, including children with initially low iron reserves that have become depleted during the milk-feeding period. In older patients, for whom liquid iron medication is indicated or preferred, Mol-Iron Liquid corrects all types of hypochromic anemias including those resulting from chronic bleeding, nutritional deficiency, pregnancy, etc.

DOSAGE AND ADMINISTRATION: In children:

Birth to 2 years. 1/2 teaspoonful three times daily

2 to 6 years... 1 teaspoonful twice daily

6 to 12 years... 1 teaspoonful three times daily

In adults:

For optimal therapeutic effect—2 teaspoonfuls three times daily.

For maintenance therapy, dosage can be relatively lower as indicated by therapeutic need.

Mol-Iron Liquid should be administered in a small quantity of water or fruit juice, not in milk.

HOW SUPPLIED: In bottles of 12 fluid ounces.

PRODUCER: White Laboratories, Inc., Newark 7, N. J.

NATESTRIN TABLETS

PURPOSE: Indicated primarily in the control of symptoms of the menopause, senile vaginitis, kraurosis vulvae, and pruritis vulvae.

COMPOSITION: Each red-coated tablet contains naturally occurring equine estrogens (estrone, estradiol, equilin, equilin, and hippulin) physiologically equivalent to 1 mg. of estrone. Natestrin contains in an amorphous (noncrystalline) form the water-insoluble mixed estrogen steroids obtained by acid hydrolysis from the urine of pregnant mares.

DOSAGE AND ADMINISTRATION: Usual dosage is one tablet daily, but may be increased to 2 or more daily, according to individual requirements.

HOW SUPPLIED: Bottles of 100, 500, and 1,000 tablets.

PRODUCER: The Upjohn Company, Kalamazoo 99, Mich.

LIAFON SQUIBB

PURPOSE: In the treatment of iron deficiency anemias and/or macrocytic anemias associated with malnutrition, pregnancy, pellagra, and sprue. Also as an adjunct to parenteral liver therapy in Addisonian pernicious anemia.

COMPOSITION: Each Liafon capsule contains: Ferrous

sulfate exsiccated, 2 gr. (approximately equivalent to 2.85 gr. ferrous sulfate); folic acid, 1.67 mg.; ascorbic acid, 50 mg.; desiccated whole liver, 0.5 gm. (approximately equivalent to 2 gm. whole fresh liver).

INDICATIONS FOR USE: In cases in which it is impossible to categorize the anemia, and for patients in whom more than one form of anemia is found or suspected.

ADMINISTRATION AND DOSAGE: Three to six capsules daily, or more, as indicated, orally.

HOW SUPPLIED: Bottles of 100 and 1,000.

PRODUCER: E. R. Squibb & Sons, New York 22, N. Y.

FLO-CILLIN

PURPOSE: A new form of parenteral penicillin.

COMPOSITION: Flo-cillin contains 300,000 units of procaine penicillin per cc. in a vehicle containing 98 per cent peanut oil and 2 per cent aluminum monostearate. Each 300,000 units contains the equivalent of 120 mg. procaine base.

DESCRIPTION: Features a permanent suspension which insures even dosage. Flo-cillin is semi-solid at room temperature, but will, when rapped slightly, go into a liquid state and can be drawn easily into a syringe.

HOW SUPPLIED: In 10 cc. vials and soon in a 1 cc. disposable eartridge, for use with the B-D Disposable Syringe or the B-D Metal Syringe.

PRODUCER: Bristol Laboratories, Inc., Syracuse, N. Y.

LIPO-ADRENAL CORTEX

PURPOSE: Treatment of Addison's disease; prophylaxis in surgical removal of cortical tumors; increasing resistance to fatigue and stress conditions such as toxemias, infections, and extensive tissue injuries caused by trauma, burns, or surgical procedures.

COMPOSITION: Each cc. contains 40 rat units (Survival-Growth) and is standardized by the Muscle-Work test to be equivalent to 2 mg. of 11-dehydro-17-hydroxycorticosterone. Chlorobutanol, 5 mg. per cc.

DESCRIPTION: Biologically standardized preparation of the steroid hormones of the adrenal cortex dissolved in vegetable oil.

DOSAGE AND ADMINISTRATION: Usual daily maintenance dosage level is 1 to 2 cc., but amount required is governed by response of the patient. In Addisonian crisis or in presence of infection or other serious complications, 2 to 5 cc. or more daily may be required. Administered intramuscularly.

HOW SUPPLIED: In 5 cc. vials.

PRODUCER: The Upjohn Company, Kalamazoo 99, Mich.

Leaves from a Doctor's Diary

By MAURICE CHIDECKEL

May 1 . . . His face aglow he sat in rapt attention and gazed happily into space. I am speaking to Dr. Grover Curry. Was he happy because his diagnosis of pulmonary carcinoma was histologically confirmed? Not at all. Did he ever diagnose a case incorrectly? Isn't he always right? And are not the men who disagree with him always lacking, deplorably so, in efficiency?

The elderly, pronounced bachelor met me at the door with a face wreathed in smiles. He took my hand and spoke feelingly: "A happier man than I does not exist. Are you listening? Think of it. In three hours from now I will be a married man." He sat down, rose and paced the room in big strides, then stopped short, and spoke again: "What a poignant loss of happiness, what an impoverishment of one's inner life when one is not married. Love. It's rejuvenating and regenerating. Let's be gay. I'll tell you a story I heard today. You'll laugh yourself silly. Two men were committed to an insane asylum, one with acute mania. The woman he was to marry and whom he vehemently loved eloped with another man on the very day he was to marry her. The one next to his cell, hopelessly insane, was the man she married!" He laughed heartily at his words.

He consulted his watch. "Time to dress. Wait. I'll call her up. Say 'hello' to her. She always did like you." He called and called, and called again. There was no answer. Then his 'phone rang. It was the minister who is, or rather was, to perform the marriage ceremony. "Please do not come. Deeply regret to inform you that Miss Louella Scott was just married to Dr. Bond. It was at the lady's request that this call is made to spare you embarrassment." For a few minutes Dr. Curry stood as if in a daze. Then he

threw his head back and laughed. But now his laughter was frightening, almost soul harrowing.

Well, my patient, plumber Copson, is of a different caliber. He called the mental institution to inquire if they don't miss a lunatic. His wife eloped with another man.

* * *

May 4 . . . "The man who commercializes the medical profession should be expelled from it." These words were uttered by Dr. Marion. After that he began to scrub for an ectopic. As he vigorously rubbed his hands with the brush he was informed that the husband of the lady is very wealthy. Quickly he dried his hands, rushed out into the corridor to inform the husband that the operation will cost him five times more than was originally agreed upon. Reminds me of a sign on an "Eatery" in Nevada: "Prices subject to change while eating."

* * *

May 6 . . . Dr. Rogers Mark is 84 years young. Full of vigor and laughter he continues his large practice as a cardiologist, and an excellent heart man he is. He overtook me in the corridor of the clinic. "I have just demonstrated a case of tetralogy of Fallot. Well, we call it a beautiful case. But what about the unhappy parents, and what about the boy himself?" Suddenly he smiled. "Somehow the world does not proclaim my greatness. You know why? Because I am not great. Well, the great military genius of Napoleon was not fully recognized. His head never appeared on a postage stamp. He was only licked at Waterloo."

* * *

May 8 . . . What a different character from Dr. Mark is Dr. Titus Lee. No one questions his diagnostic acumen, but of what narrow

mental horizon. Every one living is inferior to him. "I am," he once told me, "not unlike Abraham the patriarch. He looked for ten righteous men in Sodom, and didn't find them. I am looking only for one, one unpretentious, skilled observer like myself. I haven't as yet found one. I tremble to think what will become of our diagnostic clinic after I am gone." And his wife. She too is supreme in her estimation. "I saw your wife yesterday," I related to the irreplaceable gentleman, "I tipped my hat, but she didn't know me." He said: "Yes, I know. She told me." Well, doctor, don't grieve. The cemeteries are full of people who thought themselves indispensable. They vanished into oblivion, and their places were taken by other and better men. The doctor and his wife are both obese, and the fat of the land do not always make the fit of the land.

* * *

May 11 . . . As if things conspired to plague the life of colleague Russell Brewster. He was to receive a huge sum of money for treating a wealthy patient with streptomycin for tuberculosis. The anaphylactic reaction manifested by the patient forced the doctor to discontinue the treatment. The anaphylaxis was credited to him, and the patient is now being treated by someone else.

The woman he treated for diabetes, and diabetes only, was found to be suffering also from tuberculosis. The discovery was not made by him. The prominent socialite developed uremia after the administration of sulfa drug, and she is now flirting with the angels, for which the good doctor is given full credit. Also looking heavenward is the lady with agranulocytosis after she was treated by the doctor with thiouracil for thyrotoxicosis. I hardly recognized him when I met him a few days ago. It was his wife who prevailed on him to take a trip to South America for relaxation.

I went to the steamer to bid them *bon voyage*. His wife must have bought out a department store. The

tired doctor, afraid to trust the porters, carried innumerable bundles to their cabin. Of a sudden he let out an exclamation of horror. "Darling," his wife inquired anxiously, "have you forgotten something?" "Yes," he answered. "I forgot the piano. No. I am not crazy. I left the tickets on top of it." The ship was about to sail and it was too late to get the tickets. Back he carried the bundles, and the trip was never made.

I am wondering if absentmindedness is not hereditary. He himself told me once of his father, a philosophy professor. The elderly gentleman was present at a social gathering. "Do you remember, professor," a lady asked him, "that many years ago you asked me to marry you?" "Yes, yes," the professor spoke excitedly, "what happened? Did you marry me?"

May 15 . . . Absentmindedness. "Come up with me," said Dr. Walter Hughes. "I want to show you a case you don't see every day, a case of ataxia. It's probably of the hereditary cerebellar type in a girl of 12. This is the second case in my practice. The first sign here was scoliosis. Just see her claw feet, the loss of position sense in the toes . . ." He stopped talking.

We entered a foul-smelling hallway with rickety floor and steps. The windows were shattered, fallen plaster everywhere, and the ceiling appeared as if it was just waiting for us to enter. "Those damnable landlords," the doctor thundered, "only prompted by cold self interest. This rat hole is a disgrace to our community and a positive menace to health and life. I'll teach that dog a lesson he'll never forget . . ." He rushed over to the corner drugstore and through the phone demanded of the health department to locate and arrest the owner of that building. He was assured quick action.

Today I had to post bail for him. He looked a pitiable but a comical figure in the lock-up, flanked by two bums. As I drove him home

he looked perturbed. "I forgot I own about a dozen of those skan-ties. My lawyer bought them for me about ten years ago and he is managing them. Some management. He was here five minutes before you came. Do you know what he told me? He told me not to worry. His clients don't spend one minute longer in jail than is absolutely necessary. Damn him too." I asked: "How about that ease of ataxia?" "Hm," he retorted. "In a time like this who cares for ataxia. Besides what does one profit by such rare cases. You and I may not see another one. Do you think they know about my case in the hospital? Imagine me in the lock-up."

May 25 . . . Minor events of ten days. Orthodox widower Abraham Glusikov, age 82, refused treatment for an enlarged thyroid because a doctor told him that a man with a small thyroid can never become a father, and he just must have a son. He is the father of five daughters. Orthodox Jews must have a son to say the "kadosh," the prayer for the dead, for eleven months, in order to keep the corpse out of a hot spot. Glusikov married a girl of 22 and he did have a son. (Did he?)

Since he read that Jamaican natives were free from gingivitis because they gnaw sugar cane, my neighbor Dentist Quillan filled a whole warehouse with sugar cane and is amassing a fortune by his advertisement of a guarantee of dental and intradental hygiene and the absolute certainty of white and beautiful teeth. Patient Fowler sat in my office and gnawed sugar cane for the healthy development of his dental plates.

Oral penicillin broke up the domestic bliss of Harvey Turner. The antibiotic blackened his tongue. His wife's brother, imitating Harvey's voice, called to ask the doctor how much longer he has to take the drug. He was told that as he is suf-

fering from gonorrhea he may have to be injected with penicillin.

Harry Middleton is in a hospital with a fractured acetabulum because of coitus interruptus. Having been surprised by the husband he jumped through the second floor window.

The two women are aware of their husband's unfaithfulness. They sat in my office (they came for nervousness) and talked. Said Mrs. Turner to Mrs. Middleton: "The only woman who is certain that her husband does not cheat is the widow." Said Mrs. Middleton to Mrs. Turner: "My husband was in love with me. Well, love is like a hot bath. The longer you sit in it, the cooler it gets." After that they began to assassinate a few characters. "Did you hear about Mrs. Pincus, you know the Jewish lady who lives next door to us?" (This from Mrs. Middleton.) "Well, her husband took out the ear last night to give Mr. Youdelewitz a ride. This morning she went to the ear and discovered that Mr. Youdelewitz forgot his brassiere"—she bent over and whispered "and the snuggles." They both forgot their troubles and laughed loud and heartily.

"I can cure any form of mental retardation with massive doses of glutamic acid," spoke young Dr. Donnel enthusiastically. "Then, darling," his wife inquired, "why don't you take it yourself?"

Chronic arthritis. Chaulmoogra oil. Chronic arthritis. Oh yes, there was a change. Gastrointestinal disturbances.

Always anxious to disgorge his knowledge, Dr. Rocco spoke to Catalina about the latter's wife's gastroenteritis: "Well, I searched and searched and so far could not find the salmonella, the shigella, the colon bacilli, nor the protozoa." "Come on," said the husband, "I'll find them for you. I got a flashlight."

Subject Index

VOLUME III

ABSCCESS, acute retropharyngeal, 168; subphrenic: roentgen diagnosis, 108

Acromegaly, 452

Allergy, and bronchial asthma, 271; and headache, 25; as cause of migraine, 22; as cause of sino-nasal headache, 24; new drugs in treatment of allergic disease, 92; to drugs: diagnosis, 278

Aluminum hydroxide and/or magnesium trisilicate and calcium carbonate as seen gastroscopically, 41

Amino acids vs. plasma as intravenous protein food, 267

Amputation for diabetic gangrene, 204

Anastomosis, primary, after resection of lesions of left colon, 85

Anemia, diagnosis and treatment of various types, 441

Anesthesia, drugs and methods for occasional anesthetist, 77; spinal: hazards for occasional anesthetist, 83

Anorexia nervosa, anterior-pituitary insufficiency, Simmonds' cachexia and Sheehan's disease, 237

Antacids, and physical therapy: gastroscopic demonstration of clinical and local effects, 31; *see also* Aluminum hydroxide; Calcium carbonate; Gastric mucin; Magnesium trisilicate; criteria for effectiveness, 46

Antibiotics, *see also* Penicillin; Streptomycin; in treatment of allergic diseases, 93

Antihistamine, *see* Histamine

Anxiety, *see* Psychosomatic medicine

Appendicitis, acute, complicated by intussusception, 283

Arm, shoulder-hand syndrome in reflex dystrophy of upper extremity, 359

Arteritis, temporal, 26

Asthma, bronchial: differential diagnosis and management, 271; penicillin treatment, 94

Atrial septal defect, pathology, 336; physiologic considerations, 321

BACTEREMIA, streptomycin treatment, 294

Benadryl in treatment of allergic diseases, 100

Blood, infection: streptomycin treatment of bacteremia, 294; in transmission of infectious hepatitis, 248; loss, *see* Hemoptysis

Blood pressure, high (arterial) as cause of headache, 26

Bone, accelerated maturation with macrosomia genitalis, 460; diseases associated with endocrine dysfunction: differential diagnosis, 462; fibrous dysplasia with hypogenitalism, 458; fractures due to osteogenesis imperfecta, 456; pathologic conditions associated with endocrine dysfunction, 449

Brain surgery: orbital prefrontal lobotomy in treatment of mental illness, 179

Brucellosis, streptomycin treatment, 295

Buerger's disease, *see* Thromboangiitis obliterans

CALCIUM CARBONATE, gastroscopic appearance, 41

Cancer, biologic problem, 1; mule-spinners' carcinoma of scrotum, 163; of colon: roentgen diagnosis of obstruction due to, 107; of esophagus, 192; of left colon: resection and primary an-

astomosis for, 85; of lung, 427; of stomach: gastroscopic diagnosis vs. roentgen examination, 31, 32, 33, 35; of stomach: procedures for reducing mortality, 6; of thyroid treated with radioactive iodine, 420; research teamwork, 3

Carcinoma, *see* Cancer

Cardiac *see* Heart

Cardiospasm, diagnosis and treatment, 13

Children, respiratory emergencies in, 165

Chloroform, administration by occasional anesthetist, 81

Cholecystography in diagnosis of stones and tumors, 114

Colon, cancer: roentgen diagnosis of obstruction due to, 107; diverticulum: roentgen diagnosis of rupture, 107; resection and primary anastomosis for lesions of left portion, 85

Cyclodialysis in treatment of glaucoma, 407

DERMATITIS, contact, as manifestation of drug allergy, 279

Diabetes mellitus, complications: modern treatment of diabetic gangrene, 199

Diagnosis, differential, of bone disease associated with endocrine dysfunction, 462; mistaken, of heart disease: role of xiphosternal crunch, 109

Diathermy, short-wave, in treatment of atrophic gastritis and peptic ulcer, 36

Diphtheria, respiratory emergencies in, 168

Drainage, subconjunctival, in treatment of glaucoma, 405

Drug allergy, 278

Ductus arteriosus, patent: pathology, 339; patent: physiologic considerations, 321

Duodenum ulcer, *see* Peptic ulcer

Dwarfism, pituitary (Lorain-Levi), 455

Dysphagia due to cardiospasm, 13

Dyspnea, chronic, and recurrent hemoptysis, due to silicotuberculosis, 27

Dystrophy, reflex of upper extremity: shoulder-hand syndrome in, 359

EDEMA in patients with anorexia nervosa, 243

Eisenmenger complex, distinguished from tetralogy of Fallot, 334

Elephantiasis and scrotal edema, 159

Emergencies, respiratory, 165

Endocarditis, streptomycin treatment, 294

Endocrine glands, dysfunction associated with bone pathology, 449

Ephedrine and derivatives in treatment of allergic disease, 92

Epididymitis as cause of scrotal edema, 162

Epilepsy, bacteriologic, etiologic, and serologic studies in epilepsy and schizophrenia, II: effects in animals following inoculation of alpha streptococci, 124; III: cutaneous reactions to intradermal injection of streptococcal antibody and antigen, 367

Epinephrine in treatment of allergic diseases, 92

Ergotamine tartrate, treatment of migraine, 21

Esophagus, carcinoma, 192; cardiospasm, diagnosis and treatment, 13

Ether, administration by occasional anesthetist, 81
Experimental medicine: effect of alpha streptococci on nervous system of animals, 124
Eye disease: advances in treatment of glaucoma, 399

FEEDING, parenteral, in surgical treatment of intestinal fistula, 265
Filariasis as cause of scrotal edema, 159
Folic acid, experimental treatment of cancer, 6; treatment of macrocytic anemias, 446
Foreign bodies as cause of respiratory emergencies, 168
Froehlich's syndrome, *see* Pseudo-Froehlich's syndrome

GALLBLADDER calculi and tumors; diagnosis by cholecystography, 114
Gangrene, diabetic; modern treatment, 199
Gastric, *see* also Stomach
Gastric ulcer, *see* Peptic ulcer
Gastric mucin plus aluminum hydroxide with magnesium trisilicate in treatment of peptic ulcer, 45
Gastrointestinal tract, disorder due to anxiety, 357
General practice, psychology for general practitioner, 255
Genitalia, *see* also Scrotum; hypogenitalism with fibrous dysplasia of bone, 458; macroscopia genitalis with accelerated bony maturation, 460
Gastroscopy in diagnosis of gastric disease, 31
Glaucoma, advances in treatment, 399
Glottis edema, respiratory emergencies due to, 167
Goniotomy in treatment of glaucoma, 407
Gynecology, psychosomatic aspects, 423
Gynergen, *see* Ergotamine tartrate

HAND, shoulder-hand syndrome in reflex dystrophy of upper extremity, 359
Headache, chronic vascular, 19
Heart disease, congenital: pathologic review, 327; congenital: physiologic considerations, 321; streptomycin treatment of endocarditis, 294; sounds: xiphosternal crunch as cause of mistaken diagnoses of heart disease, 109
Hematocle, true and spurious, 159
Hemoptysis and chronic dyspnea due to silico-tuberculosis, 27
Hepatitis, infectious: diagnosis and treatment, 247
Heredity and predisposition to cancer, 2
Histamine, antagonists in treatment of allergic disease, 96; headache, 23
Hormones, of doubtful value in allergic diseases, 95
Hydrocele, 157
Hypogenitalism with fibrous dysplasia of bone, 458
Hyper-, Hypothyroidism, *see* Thyroid

INDUCTOTHERMIE, treatment of peptic ulcer, 36
Infection, anemia due to, 442
Injections, parenteral feeding in surgical treatment of intestinal fistula, 265
Intestines, congenital atresia: roentgen diagnosis, 107; fistula: use of parenteral feeding in surgical treatment, 265; gener-

alized paralytic ileus: roentgen diagnosis, 105; obstruction: roentgen diagnosis, 103
Intussusception, complicating acute appendicitis, 283; roentgen diagnosis, 107
Iodine, radioactive, in study and treatment of thyroid diseases, 410
Iridectomy, in treatment of glaucoma, 407; peripheral in treatment of glaucoma, 404
Iron deficiency anemias, 442
Isotopes: radioactive iodine in study and treatment of thyroid diseases, 410

J **AUNICE** in infectious hepatitis, 249

K. **R. VACCINE**, experimental treatment of cancer, 5

LARYNGOTRACHEOBRONCHITIS, acute, as cause of respiratory emergencies in children, 169
Leukotomy, *see* Lobotomy
Liver inflammation: diagnosis and treatment of infectious hepatitis, 247
Lobotomy, orbital prefrontal, in treatment of chronic mental illness, 179
Lorain-Levi (pituitary) dwarfism, 455
Lung carcinoma: diagnosis and treatment, 427

MACROCYTIC anemia, 444
Macrosomia genitalis with accelerated bony maturation, 460
Magnesium trisilicate, gastroscopic appearance, 41
Malaria, recent advances in treatment, 171
Meningitis, streptomycin treatment, 292
Mental illness, *see* also Schizophrenia; treatment with orbital prefrontal lobotomy, 179
Metabolism, water: disturbances associated with starvation, 237; methods, and psychosomatic medicine, 353
Migraine, pathogenesis and treatment, 19
Myalgia of head, 25
Mucin, *see* Gastric mucin

NERVOUS SYSTEM, lesions due to injection of alpha streptococci in experimental animals, 124
Nitrous oxide, administration by occasional anesthetist, 81
Novocaine, *see* Procaine
Nutrition in anorexia nervosa, 237; parenteral feeding in surgical treatment of intestinal fistula, 265

OSTEOGENESIS imperfecta associated with pseudo-Froehlich's syndrome, 456
Osteopathy, *see* Bone
Ovaries, agenesis (Turner's syndrome), 453

PARENTERAL, *see* Injections

- Penicillin, antibacterial activity compared with, 286; treatment of asthma, 93
- Peptic ulcer, diagnosis and treatment, 342; gastric vagotomy for, 8; inductothermic treatment, 36; psychosomatic diagnosis, 354; transthoracic vagotomy for, 116; treatment with gastric mucin plus aluminum hydroxide with magnesium trisilicate, 45
- Pernicious anemia, 444
- Pharynx, acute retropharyngeal abscess, 168
- Physical therapy and antacids: gastroscopic demonstration of clinical and local effects, 31
- Pituitary, adenoma with acromegalic manifestations, 452; anterior, insufficiency, anorexia nervosa, Simmonds' cachexia and Sheehan's disease, 237; dwarfism (Lorain-Levi), 455
- Plasma vs. amino acids as intravenous protein food, 267
- Pneumonia, streptomycin treatment, 292
- Podophyllin, experimental treatment of cancer, 5
- Poliomyelitis, respiratory emergencies in, 170
- Polysaccharide, treatment of cancer, 5
- Pregnancy, anemia in, 446
- Procaine, administration by occasional anesthetist, 83
- Protein in parenteral feeding of patients with intestinal fistula, 266
- Pseudo-Froehlich's syndrome with osteogenesis imperfecta, 456
- Psychology for general practitioner, 255
- Psychosomatic medicine, and methods of diagnosis, 353; gynecologic applications, 423; psychology for general practitioner, 255
- Pulmonary, *see* Lung
- Pyribenzamine in treatment of allergic diseases, 100

RADIOACTIVE iodine in study and treatment of thyroid disease, 410

- Respiration, difficult, *see* Dyspnea
- Respiratory emergencies, 165
- Roentgen rays, cholecystography in diagnosing calculi and tumors, 114; diagnosis of acute abdomen, 102; vs. gastroscopy in diagnosis of gastric disease, 31

SCHIZOPHRENIA, bacteriologic, etiologic, and serologic studies in epilepsy and schizophrenia, II: effects in animals following inoculation of alpha streptococci, 124; III: cutaneous reactions to intradermal injection of streptococcal antibody and antigen, 367; treatment with prefrontal orbital lobotomy, 181

- Sclerectomy in treatment of glaucoma, 404
- Scrotum, types of scrotal enlargements, 157
- Sheehan's disease, anorexia nervosa, anterior-pituitary insufficiency, and Simmonds' cachexia, 237
- Shoulder-hand syndrome in reflex dystrophy of upper extremity, 359
- Silicotuberculosis as cause of chronic dyspnea and recurrent hemoptysis, 27
- Simmonds' cachexia, anorexia nervosa, anterior-pituitary insufficiency, and Sheehan's disease, 237
- Sino-nasal headache due to allergy, 24
- Spermatic cord, torsion as cause of scrotal edema, 160
- Spermatocele, 158

- Starvation, disturbances in water metabolism associated with, 237
- Stomach, cancer: procedures for reducing mortality, 6; disease: clinical and local effects of antacids and physical therapy as shown gastroscopically, 31; inflammation: gastroscopic diagnosis vs. roentgen examination, 31; inflammation: inductothermic treatment of atrophic gastritis, 37; ulcer, *see* Peptic ulcer
- Streptococci, alpha: effect on nervous system in experimental animals, 124; cutaneous reactions of schizophrenic and epileptic patients to intradermal injection of antibody and antigen, 367
- Streptomycin, absorption and excretion, 288; antibacterial activity compared with penicillin, 286; dosage, 289; exhibit, 285; resistance, 290; sensitivity of various organisms, 287; therapeutic effects, 291-297; toxicity, 290
- Subphrenic abscess: roentgen diagnosis, 108
- Surgery, streptomycin as adjunct in surgical infections, 297
- Swallowing, difficult, *see* Dysphagia
- Sympathetic nervous system, interruption in treatment of shoulder-hand syndrome, 359

TESTES, inflammation and tumors as causes of scrotal edema, 163

- Tests, psychologic, as aid to general practitioner, 257
- Tetralogy of Fallot, and pulmonary stenosis and atresia, 332; physiologic considerations, 321
- Thromboangiitis obliterans, diagnosis and treatment, 185
- Thyroid, disease: radioactive iodine in study and treatment, 410; hypothyroidism with osteoporosis, 450; symptoms of hyperthyroidism due to anxiety, 358
- Tissue disturbance and cancer, 4
- Tuberculosis, silicotuberculosis as cause of chronic dyspnea and recurrent hemoptysis, 27; streptomycin for adjuvant treatment, 296
- Tularemia, streptomycin treatment, 291
- Turner's syndrome, 453
- Typhoid fever, streptomycin treatment, 295

UNDULANT FEVER, *see* Brucellosis

- Urethane, experimental treatment of cancer, 5
- Urinary tract infections: streptomycin treatment, 293
- Urine extravasation as cause of scrotal edema, 161

VAGOTOMY, gastric, in treatment of peptic ulcer, 8; indications, 352; transthoracic, for peptic ulcer, 116

- Vasoconstrictors in treatment of allergic diseases, 92
- Vitamins of doubtful value in allergic diseases, 94

WATER METABOLISM, disturbances associated with starvation, 237**XIPHOSTERNAL CRUNCH**, role in erroneous diagnoses of heart disease, 109

- X-rays, *see* Roentgen rays

AUTHOR INDEX—VOLUME III

- Alexander, Harry L., Drug allergy, 278
- Baylin, G. J., *see* Grimson, K. S.
- Bergman, R. Theodore, Scrotal enlargements, 157
- Berkman, John M., Anorexia nervosa, anterior-pituitary insufficiency, Simmonds' cachexia, and Sheehan's disease: including some observations on disturbances in water metabolism associated with starvation, 237
- Bortz, Edward L., Cancer: a biologic problem, 1
- Burchell, Howard B., Congenital cardiac disease: physiologic considerations, 321
- Burlando, Adolfo J., Cholecystography in diagnosing small calculi and stones, 114
- Busch, Anthony K., *see* Smolik, Edmund A.
- Camp, Edward H., and Dragstedt, Lester R., Gastric vagotomy in peptic ulcer, 8
- Carlisle, J. Mallory, *see* Morgan, Hugh J.
- Capps, Richard B., Diagnosis and treatment of infectious hepatitis, 247
- Cohn, George M., *see* Finkler, Rita S.
- Coulter, John S., *see* Hardt, Leo L.
- Criep, Leo H., Chronic vascular headache, 19
- Curran, Edward J., Advances in the treatment of glaucoma, 399
- Custer, Monford D., *see* Waugh, John M.
- DeBakey, Michael E., and Ochsner, Alton, Carcinoma of the esophagus, 192
- DeBakey, Michael, *see* Ochsner, Alton
- De Takats, Geza, Diagnosis and management of Buerger's disease, 185
- Dixon, Leonard, *see* Ochsner, Alton
- Dragstedt, Lester R., *see* Camp, Edward H.
- Edwards, Jesse E., Congenital cardiac disease: a pathologic review, 327
- Elman, Robert, Use of parenteral feeding in the surgical treatment of intestinal fistula, 265
- Feinberg, Samuel M., Newer drugs in the treatment of allergic diseases, 92
- Finkler, Rita S., and Cohn, George M., Osteopathies encountered in the endocrine clinic, 449
- Friedman, H. Harold, *see* Steinbrocker, Otto
- Gildea, Edwin F., Psychosomatic medicine and methods of diagnosis, 353
- Gordon, Harold, ed., Clinicopathologic conference: chronic dyspnea and recurrent hemoptysis, 27
- Grimson, K. S., Baylin, G. J., Taylor, H. M., Hesser, F. H., and Rundles, R. W., Transthoracic vagotomy for peptic ulcer, 116
- Hardt, Leo L., and Coulter, John S., Clinical and local effects of antacids and physical therapy as shown gastroscopically, 31
- Hesser, F. H., *see* Grimson, K. S.
- Hofstatter, Leopold, *see* Smolik, Edmund A.
- Hunt, John S., *see* Morgan, Hugh J.
- Keating, F. Raymond, Jr., Radioactive iodine in the study and treatment of thyroid diseases, 410
- Kent, Louis R., *see* Morgan, Hugh J.
- Lahey, Frank H., Diagnosis and treatment of peptic ulcer, 342
- Lipin, Raymond J., and Miller, Joseph M., Acute appendicitis complicated by intussusception, 283
- Miller, Joseph M., *see* Lipin, Raymond J.
- Morgan, Hugh J., Hunt, John S., Kent, Louis R., and Carlisle, J. Mallory, Streptomycin exhibit, 285
- Ochsner, Alton, DeBakey, Michael, and Dixon, Leonard, Carcinoma of the lung, 427
- Ochsner, Alton, *see* DeBakey, Michael E.
- Pratt, J. P., Psychosomatic gynecology, 423
- Rosenow, Edward C., Bacteriologic, etiologic, and serologic studies in epilepsy and schizophrenia, II: effects on animals following inoculation of alpha streptococci, 124; III: cutaneous reaction to intradermal injection of streptococcal antibody and antigen, 367
- Rundles, R. W., *see* Grimson, K. S.
- Samuels, Saul S., Modern treatment of diabetic gangrene, 199
- Sante, Leroy, The acute abdomen, 102
- Shakow, David, Psychology for the general practitioner, 255
- Shannon, James A., Recent advances in treatment of malaria, 171
- Smolik, Edmund A., Hofstatter, Leopold, and Busch, Anthony K., Further observations on orbital prefrontal lobotomy in treatment of chronic mental illness, 179
- Solis-Cohen, Myer, The xiphosternal crunch; its recognition and unfortunate role in life insurance and employment rejections, 109
- Spitzer, Norman, *see* Steinbrocker, Otto
- Steinbrocker, Otto, Spitzer, Norman, and Friedman, H. Harold, The shoulder-hand syndrome in reflex dystrophy of the upper extremity, 359
- Sturgis, Cyrus C., Diagnosis and treatment of the anemias, 441
- Taylor, H. M., *see* Grimson, K. S.
- Toomey, John A., Respiratory emergencies, 165
- Unger, Leon, Differential diagnosis and management of bronchial asthma, 271
- Vinson, Porter P., Diagnosis and treatment of cardiospasm, 13
- Waters, Ralph M., Drugs and methods for the "occasional" anesthetic, 77
- Waugh, John M., and Custer, Monford D., Resection and primary anastomosis for lesions of the left portion of the colon, 85

AFTER HOURS

By FRANK G. SLAUGHTER, M.D.

Civic Club Stomach

WE HAVE BEEN conducting an important piece of research into the medical aspects of the rise of the civic club as an institution typical of American culture, and we are now ready to release our findings to a waiting world. So great was our zeal in this endeavour, that we actually went at it the hard way and joined a civic club ourselves. Now, with calluses from shaking hands, a chronic cough from being slapped on the back, anorexia from facing the pallid products of hotel chefs, laryngitis from singing "There's a long, long trail," and a chronic midday droop from the weekly hour spent sleeping through inspirational speeches, we're a physical wreck, but we have accomplished our aim. For the first time in any journal, we present a new clinical entity, namely, "Civic Club Stomach."

History records a "Stone Age," an "Ice Age," and "The Atomic Age." Now there is another, the "Age of Dyspepsia." Stomach trouble is so frequent that it is practically normal. Without burps, belches, and borborygmi we wouldn't even feel like human beings. Peptic ulcer has become the badge of success and man achieves greatness in modern civilization in direct ratio to the amount of his stomach acid. So many doctors are developing ulcers that soon we may be able to designate the relative success of physicians with "two ulcer" internists, "three ulcer" surgeons, or even "four ulcer" nose and throat men, the apogee of medical accomplishment. Pity the poor "one ulcer" man of medicine, then, the forgotten doctor.

Coincident with this change in our national digestive habit for the worse has gone a meteoric rise in civic clubs. Formerly, every large city had its Rotary

or its Kiwanis Club; now every cross-roads has a weekly club meeting around the local crackerbox to tear a herring and swap gossip. Drive through any typical American town around noon and you'll hear the pistol-shot sounds of jolly good fellows slapping each other on the back, or the yowling refrain of "Bury me not on the lone prairie." Civic America is gathering for its weekly vocation.

To prove the connection between the startling grip that dyspepsia has obtained upon the stomachs of the nation and the increase in civic clubs, we present the case history of a typical victim of "Civic Club Stomach," Elmer Jerk, a young executive:

It is Friday, "Go-Getter" Luncheon day. Already Jerk has had a fight with his wife over the dollar thirty-five they charge for the luncheon. All morning he's worried and tense, and by noon, his breakfast is still in his stomach, a lead weight of greasy egg and burnt toast, awash in stale coffee. Comes noon and Jerk rushes from his place of business to get to the hotel. If he is late he'll be fined; if he forgot to change his button when he changed suits this morning, he'll earn another fine. By the time he reaches the meeting, and locates a seat at a table in the far corner where he can sleep peacefully, he's not only in a fine state of nerves, but punchdrunk from backslaps and handshakes. But does he get to eat in peace? Indeed not!

First, a character with a songbook insists that he "Pack up your troubles in your old kit bag, and smile, smile, smile." Elmer Jerk has been packing his troubles into his stomach since he and the little woman started out with the row this morning and the old kit bag feels like it's going to explode any minute. And he has heartburn down to his toes. But he's paying a dollar thirty-five for this repast and he's got to get his money's worth, so he guiltily begins on his fruit cocktail before the singing is ended, and starts hunting for the dressing on his salad. If he doesn't get a running start, he knows he'll never get to his dessert before the speech begins. Besides, while the others are reared back, lifting their voices in song, he can have a little play with his elbows. Once the eating becomes general, he might as well be in a strait-jacket.

With the fruit and salad disposed of, Elmer licks his chops and prepares for the main course. Maybe this time they'll have something he really likes. He sniffs and cranes his neck to see the

waiters. It looks like . . . Could it be? . . . His gastric juices start pouring out in anticipation of the feast. Shivers of smooth muscle contraction run up and down his digestive tract. And then . . . THUD! . . . His spirits fall, his pylorus tightens, and his gastric flow is cut off in midstream. Roast beef again! And green peas!

BUT JERK is no quitter; he's in there with the old college try and even mops up the last drop of gravy with his roll. (Where else but a civic club dinner would he find a roll that would absorb exactly one drop of gravy?) His stomach is quivering like the cherry jello that winds up the repast, but Jerk shoves it down and clasps his cardia tight behind it. Now for a nice quiet nap.

But the speaker today is dynamic; he took the Dale Carnegie course. Just as Jerk gets to dozing well, the shout of "WAR!" rings in his ears and he comes bolt awake, heart pounding, sweating, and diving for a foxhole under the table. He recovers, gets a grip on himself with considerable difficulty, and manages to drift back into slumber when the stentorian cry of, "THE RUSSIANS!!!" tears his nervous system completely apart.

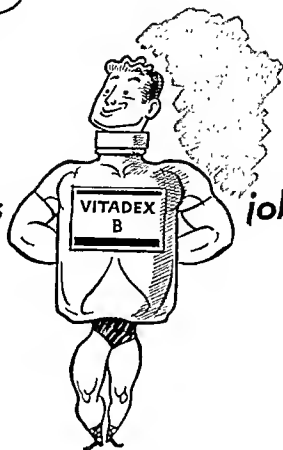
A quivering hunk of jello-filled humanity now, Jerk sits there trembling and gnawing at his fingernails. A glance at his watch tells him its two minutes until quitting time, but the speaker is going strong now, exploding atomic bombs right and left. He reaches the zero hour, he passes it without pausing, and Jerk breaks out in a cold sweat again, remembering the dressing down he got from the boss the last time he was late. Around him, at table after table, strong men are turning pale and looking furtively for the exit. The wheels of commerce and industry are slowing. Five minutes more and paralysis will grip the city as key man after key man keels over in his chair with a heart attack or a perforated ulcer from the strain.

Then, finally, the speaker is through. The spatter of applause is drowned by the thunder of running feet. Panting mankind tears through the hotel lobby and up the street. Jerk is out in front, but he's wobbly. He makes it to his desk with a sigh of relief and sinks, panting, into the chair. The stenographer with the short dress crosses her knees, but Elmer doesn't look. The gal with the peek-a-boo blouse passes, but he doesn't even peek. Poor Jerk . . . he is dead.

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*Sebrell, W. H., Jr., et al: J. Pediat. 22:494-507, April, 1943.



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ALL AFTERNOON the roast beef, green peas, and cherry jello lie there on top of greasy egg, burnt toast and coffee. Elmer begins to feel a gnawing pain in his midriff. By five o'clock he's in a bad way, for there's still the angry little woman at home. He stops off at the bar for a quick one to fortify him, at sixty cents, and by the time he reaches home he's dragging a stomach that weighs a hundred pounds. He opens the door and staggers in, bowing his head for the bludgeon.

"Why dar-r-r-ling!" Can this be the same little woman? "Is that you?"

"If she only knew," Elmer groans to himself. He'll never be the same.

"See anything different?" she coos.

"Er, ah . . ."

"I bought a new hat." She comes provocatively close to him. (What a time for sex to rear its head!) "I just had to, after that quarrel we had this morning. Isn't it beautiful. And only nineteen, ninety-five."

"Yes dear. It's beau. . . ." Elmer gulps, puts his hand over his mouth and runs for the bathroom in a photofinish with his spastic pylorus. Gulping icewater

afterwards, he makes a quick mental calculation. A dollar, thirty-five for the lunch, sixty for the drink, nineteen ninety-five for the hat. Twenty-one ninety for one civic club luncheon. No wonder he's got indigestion! Pretty soon he'll have an ulcer. But that won't help him any. They've got a "Milk and Crackers" club for those who can't eat roast beef.

ELMER JERK is a simple case. Some people belong to two civic clubs! Think what their stomachs must look like. Case after case could be cited of the great American disease, "Civic Club Stomach," but we have other findings to report. In the course of our studies we have unearthed a number of less obvious syndromes, which are nevertheless typical and frequent in occurrence.

"Rotary Right" is a spastic condition of the right hand and forearm, in the position for shaking hands. Sufferers from this condition are in great demand as greeters. "Kiwanis Knee" is a bursitis from bumping your knees against the legs of hotel diningroom tables. "Civitan Cough" is a chronic gasping intake of breath, from being slapped on the

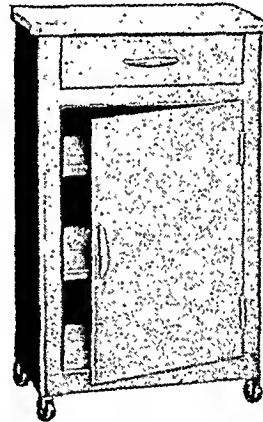
back. "Lions Larynx," is a very common condition, and comes from singing off-key. "Optimist Ogle" is a peculiar squinting movement accompanied by a sudden stooping, resulting from peering at identification badges to read the names of people you don't remember. "Exchange Club Elbow" is another spastic condition in which the elbows are held rigidly at the sides, from eating in too close quarters at civic club luncheon tables.

The most startling of these occupational diseases of civic club members, however, is "Beef Berserk," characterized by agonizing cries of, "No! Not that!" at the sight of a plate of roast beef.

In view of these findings, it should be apparent to everyone that the civic clubs exert a profound effect upon the health of the American male, one which must be taken into consideration very seriously, if we are not to overlook important and dangerous illnesses.

Great Scot! It's Friday noon!!!

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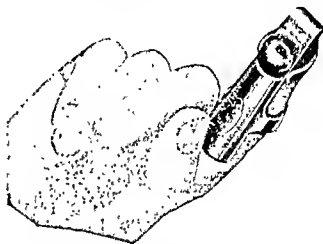
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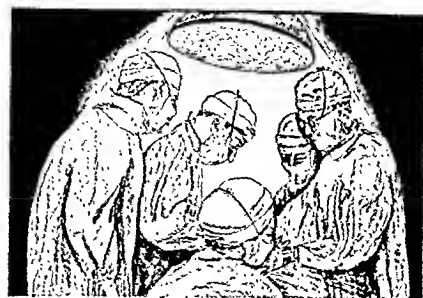
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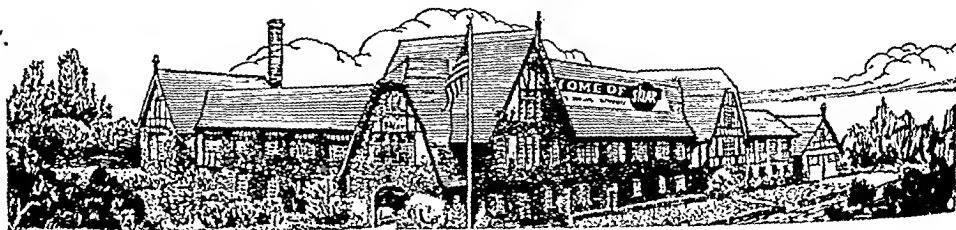
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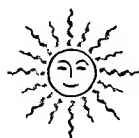


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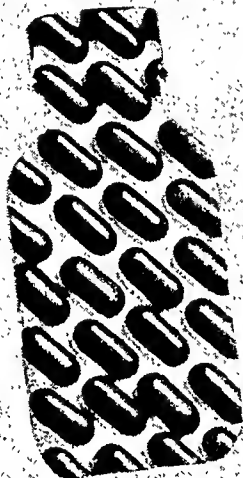
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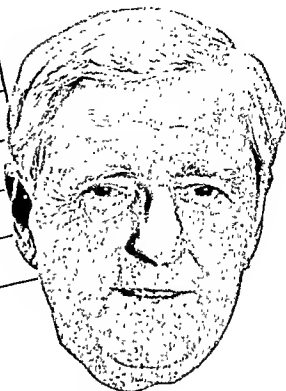
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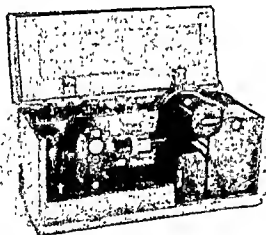
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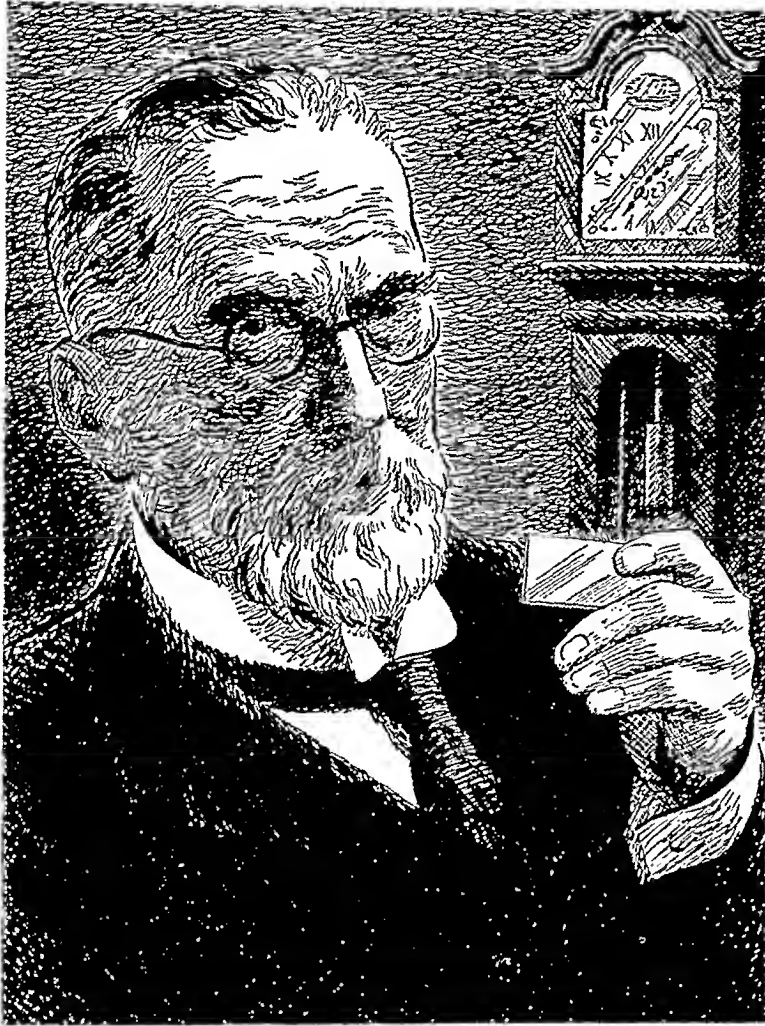
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Paul Ehrlich, expanding on his knowledge gained as a pupil of Koch, concluded from his experiences in the staining of bacteria that there was a close chemical affinity between the cellular body and the stain. This idea led him to believe that specific drugs could be found which would kill invading pathologic organisms, without damage to the host. His conclusions helped create the science of chemotherapy, which is increasingly important today.

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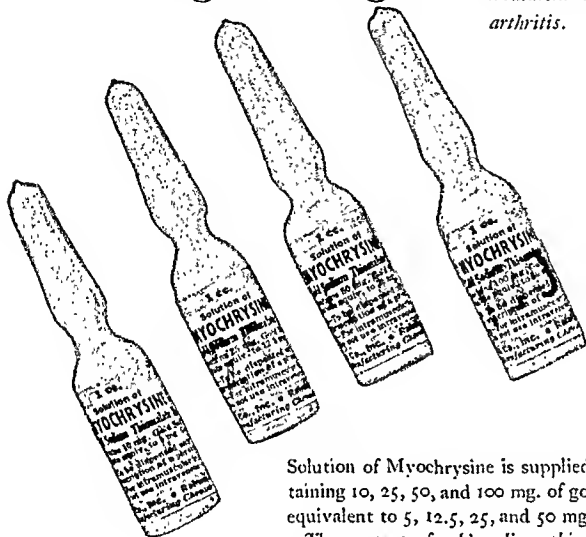
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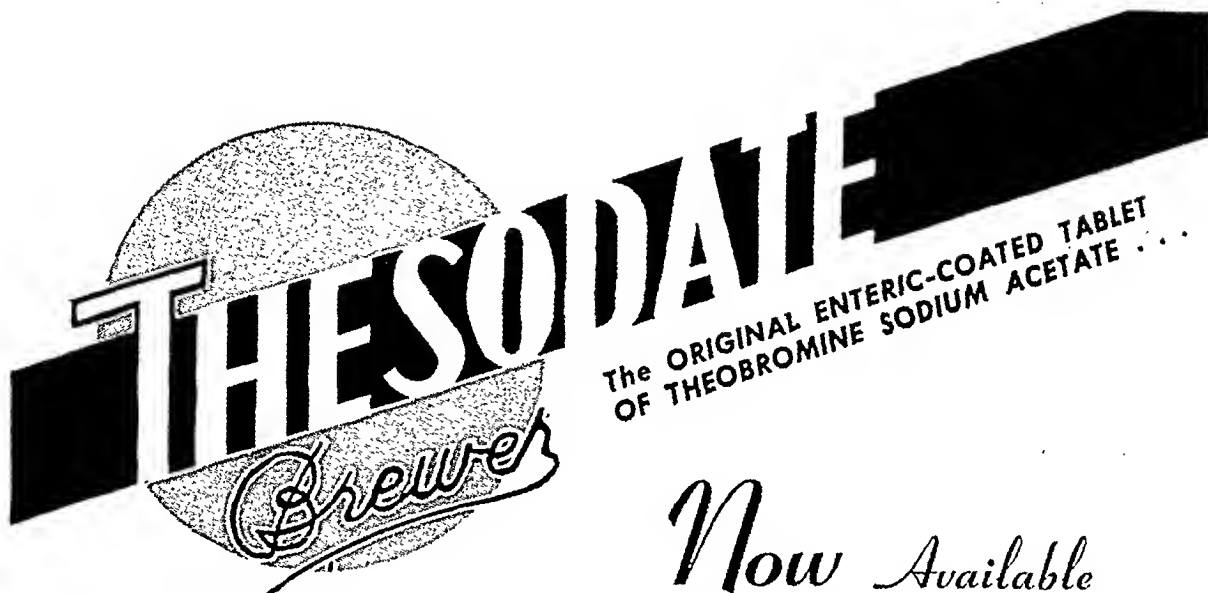
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for the treatment of active rheumatoid arthritis

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the protection of **RUTIN**

the action of **AMINOPHYLLINE**

the sedation of **PHENOBARBITAL**



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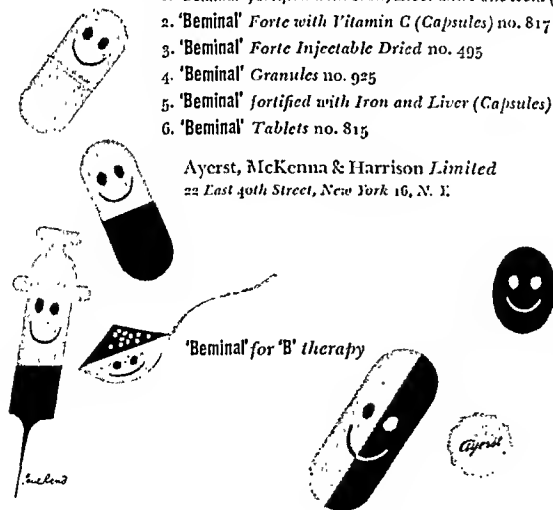
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the protection of **RUTIN**

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the sedation of **PHENOBARBITAL**



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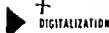
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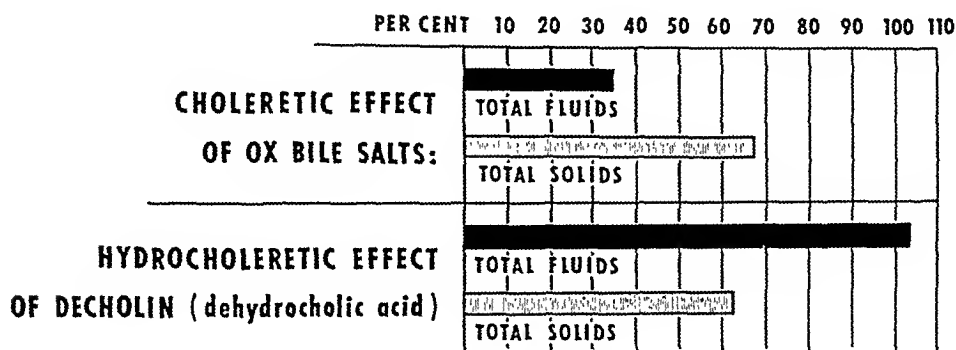
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Ivy, A. C., et al: Am. J. Dig. Dis. 7:333 (Aug.) 1940.

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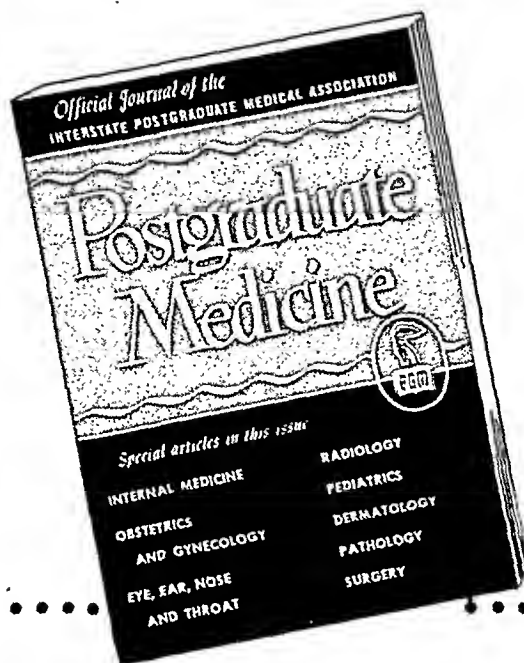
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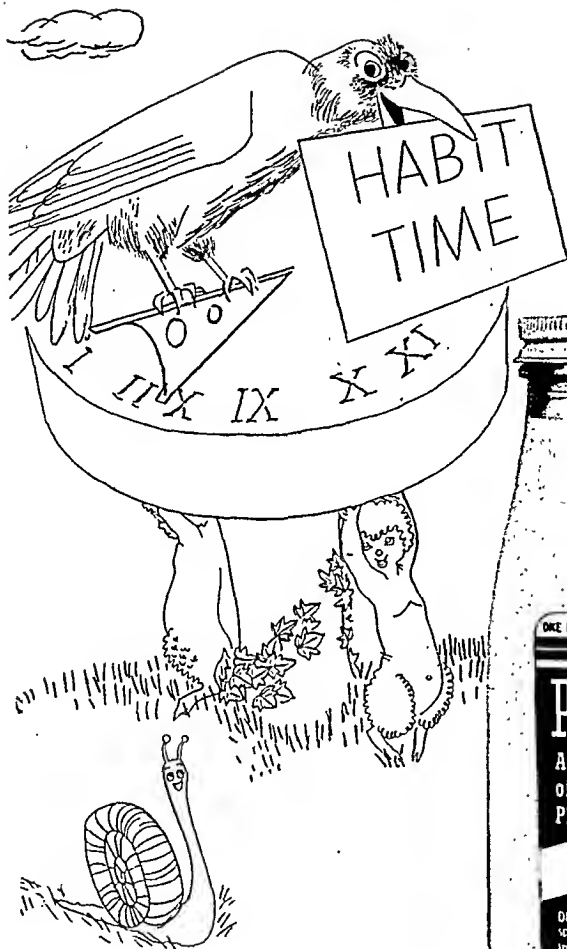
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